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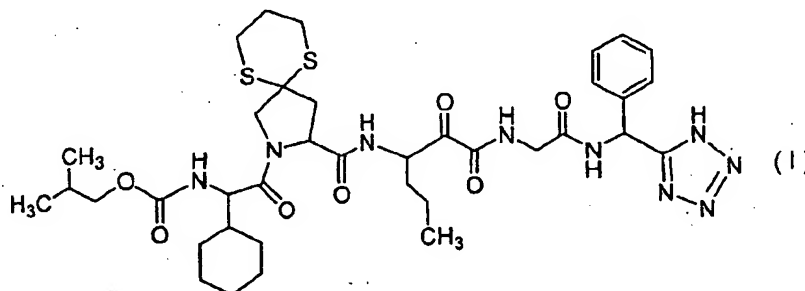
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(54) Title: DIARYL PEPTIDES AS NS3-SERINE PROTEASE INHIBITORS OF HEPATITIS C VIRUS



(57) Abstract: The present invention is directed to certain diaryl amide compounds as NS3-Serine protease inhibitors of hepatitis C virus. A particularly preferred compound is of the formula (I).

WO 02/48172 A2

**DIARYL PEPTIDES AS NS3-SERINE PROTEASE INHIBITORS OF HEPATITIS
C VIRUS**

FIELD OF INVENTION

The present invention relates to novel hepatitis C virus ("HCV") protease inhibitors, pharmaceutical compositions containing one or more such inhibitors, methods of preparing such inhibitors and methods of using such inhibitors to treat hepatitis C and related disorders. This invention specifically discloses diaryl peptide compounds as inhibitors of the HCV NS3/NS4a serine protease.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) is a (+)-sense single-stranded RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH), particularly in blood-associated NANBH (BB-NANBH)(see, International Patent Application Publication No. WO 89/04669 and European Patent Application Publication No. EP 381 216). NANBH is to be distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), delta hepatitis virus (HDV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), as well as from other forms of liver disease such as alcoholism and primary biliar cirrhosis.

Recently, an HCV protease necessary for polypeptide processing and viral replication has been identified, cloned and expressed; (see, e.g., U.S. Patent No. 5,712,145). This approximately 3000 amino acid polyprotein contains, from the amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins (NS1, 2, 3, 4a, 5a and 5b). NS3 is an approximately 68 kda protein, encoded by approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine protease domain consisting of approximately 200 of the N-terminal amino acids; and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The

NS3 protease is considered a member of the chymotrypsin family because of similarities in protein sequence, overall three-dimensional structure and mechanism of catalysis. Other chymotrypsin-like enzymes are elastase, factor Xa, thrombin, trypsin, plasmin, urokinase, tPA and PSA. The HCV NS3 serine protease is responsible for proteolysis of the polypeptide (polyprotein) at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions and is thus responsible for generating four viral proteins during viral replication. This has made the HCV NS3 serine protease an attractive target for antiviral chemotherapy.

It has been determined that the NS4a protein, an approximately 6 kda polypeptide, is a co-factor for the serine protease activity of NS3. Autocleavage of the NS3/NS4a junction by the NS3/NS4a serine protease occurs intramolecularly (*i.e.*, *cis*) while the other cleavage sites are processed intermolecularly (*i.e.*, *trans*).

Analysis of the natural cleavage sites for HCV protease revealed the presence of cysteine at P1 and serine at P1' and that these residues are strictly conserved in the NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions. The NS3/NS4a junction contains a threonine at P1 and a serine at P1'. The Cys→Thr substitution at NS3/NS4a is postulated to account for the requirement of *cis* rather than *trans* processing at this junction. See, *e.g.*, Pizzi *et al.* (1994) Proc. Natl. Acad. Sci. (USA) 91:888-892, Failla *et al.* (1996) Folding & Design 1:35-42. The NS3/NS4a cleavage site is also more tolerant of mutagenesis than the other sites. See, *e.g.*, Kollykhalov *et al.* (1994) J. Virol. 68:7525-7533. It has also been found that acidic residues in the region upstream of the cleavage site are required for efficient cleavage. See, *e.g.*, Komoda *et al.* (1994) J. Virol. 68:7351-7357.

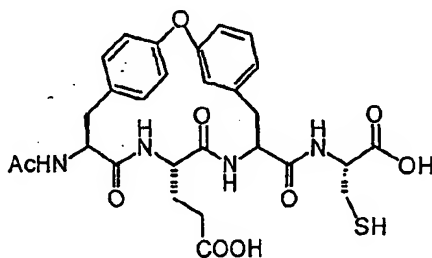
Inhibitors of HCV protease that have been reported include antioxidants (see, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (see, International Patent Application Publication No. WO 98/17679, Landro *et al.* (1997) Biochem. 36:9340-9348, Ingallinella *et al.* (1998) Biochem. 37:8906-8914, Llinàs-Brunet *et al.* (1998) Bioorg. Med. Chem. Lett. 8:1713-1718), inhibitors based on the 70-amino acid polypeptide eglin c (Martin *et al.* (1998) Biochem. 37:11459-11468, inhibitors affinity selected from human pancreatic secretory trypsin inhibitor (hPSTI-C3) and minibody repertoires (MBip) (Dimasi *et al.* (1997) J. Virol. 71:7461-7469), cV_HE2 (a "camelized"

variable domain antibody fragment) (Martin *et al.* (1997) *Protein Eng.* 10:607-614), and α 1-antichymotrypsin (ACT) (Elzouki *et al.*) (1997) *J. Hepat.* 27:42-28). A ribozyme designed to selectively destroy hepatitis C virus RNA has recently been disclosed (see, *BioWorld Today* 9(217): 4 (November 10, 1998)).

5 Reference is also made to the PCT Publications, No. WO 98/17679, published April 30, 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, published May 28, 1998 (F. Hoffmann-La Roche AG); and WO 99/07734, published February 18, 1999 (Boehringer Ingelheim Canada Ltd.).

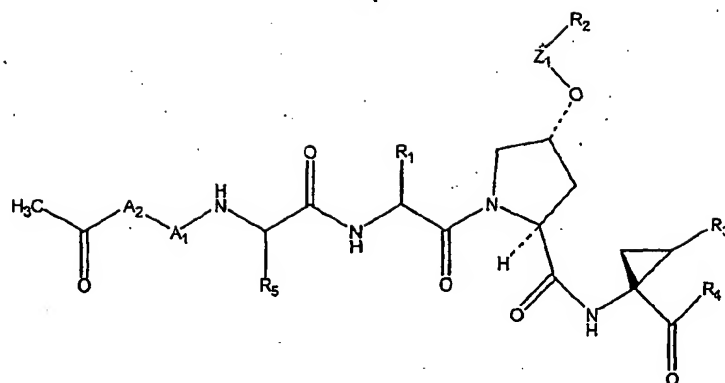
HCV has been implicated in cirrhosis of the liver and in induction of
10 hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV infection. Current data indicates a less than 50% survival rate at four years post cirrhosis diagnosis. Patients diagnosed with localized resectable hepatocellular carcinoma
15 have a five-year survival rate of 10-30%, whereas those with localized unresectable hepatocellular carcinoma have a five-year survival rate of less than 1%.

Reference is made to A. Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) describing the synthesis of bicyclic analogs of an inhibitor of HCV NS3 protease. A
20 compound disclosed therein has the formula:



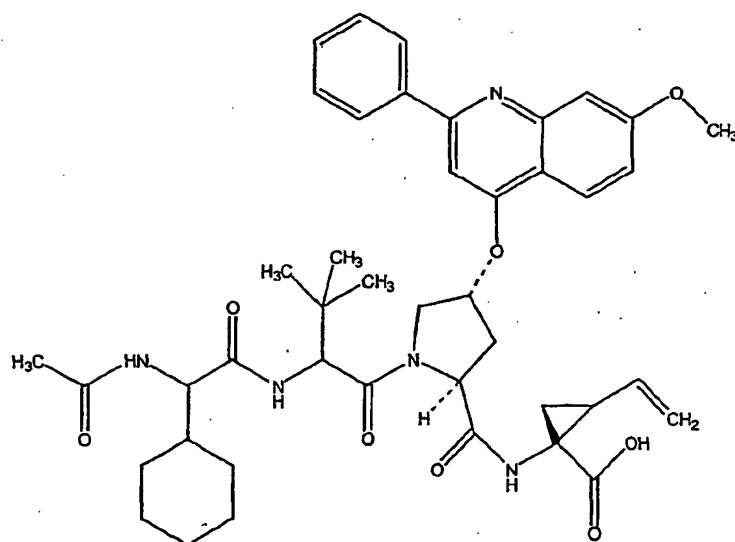
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim
25 Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:

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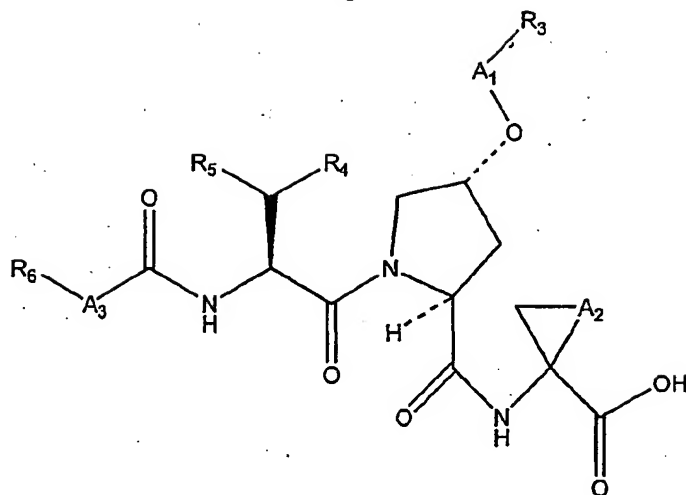
where the various elements are defined therein. An illustrative compound of that series is:

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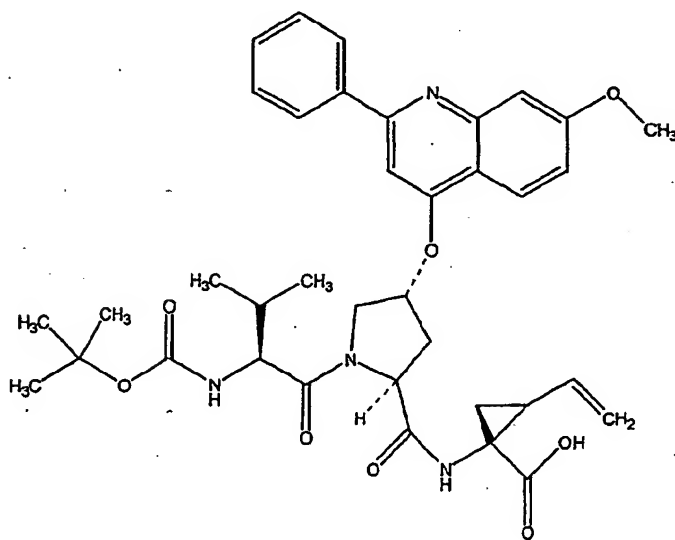
Reference is also made to WO 00/09543 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:

5



where the various elements are defined therein. An illustrative compound of that series is:

5



Current therapies for hepatitis C include interferon- α (INF $_{\alpha}$) and combination therapy with ribavirin and interferon. See, e.g., Beremguer *et al.* (1998) *Proc. Assoc. Am. Physicians* 110(2):98-112. These therapies suffer from a low sustained response rate and frequent side effects. See, e.g., Hoofnagle *et al.* (1997) *N. Engl. J. Med.* 336:347. Currently, no vaccine is available for HCV infection.

Pending patent applications, Serial No. 60/194,607, filed April 5, 2000, and Serial No. 60/198,204, filed April 19, 2000, both having common ownership with the present application, disclose certain macrocyclic NS-3 serine protease inhibitors of hepatitis C virus.

There is a need for new treatments and therapies for HCV infection. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of one or more symptoms of hepatitis C.

It is a further object herein to provide methods of treatment or prevention or amelioration of one or more symptoms of hepatitis C.

A still further object of the present invention is to provide methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

Another object herein is to provide methods of modulating the processing of the HCV polypeptide using the compounds provided herein.

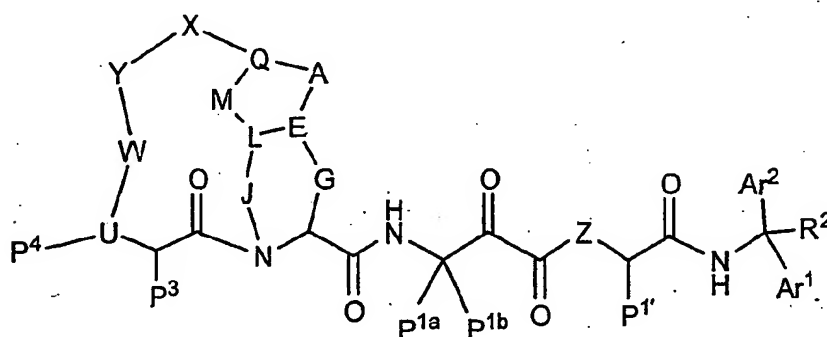
SUMMARY OF THE INVENTION

In its many embodiments, the present invention provides a novel class of inhibitors of the HCV protease, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention or amelioration or one or more of the symptoms of hepatitis C. Also provided are methods of modulating the interaction of an HCV polypeptide with HCV protease. Among the compounds provided herein, compounds that inhibit HCV NS3/NS4a serine protease activity are preferred. The presently disclosed compounds generally contain about four or more amino acid residues and less than about twelve amino acid residues. Specifically, the present application discloses peptide compounds, defined further below in Formulae I, II and III.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

In its first embodiment, the present invention provides a compound of

Formula I:



Formula I

wherein:

X and Y are independently selected from the moieties: alkyl, alkyl-aryl,
 10 heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyl ether,
 alkyl-aryl ether, aryl ether, alkyl amino, aryl amino, alkyl-aryl amino, alkyl thio,
 alkyl-aryl thio, aryl thio, alkyl sulfone, alkyl-aryl sulfone, aryl sulfone, alkyl-alkyl
 sulfoxide, alkyl-aryl sulfoxide, alkyl amide, alkyl-aryl amide, aryl amide, alkyl
 sulfonamide, alkyl-aryl sulfonamide, aryl sulfonamide, alkyl urea, alkyl-aryl urea,
 15 aryl urea, alkyl carbamate, alkyl-aryl carbamate, aryl carbamate, alkyl-hydrazide,
 alkyl-aryl hydrazide, alkyl hydroxamide, alkyl-aryl hydroxamide, alkyl sulfonyl, aryl
 sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl,
 heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxy carbonyl,
 heteroaryloxy carbonyl, alkylaminocarbonyl, arylaminocarbonyl,
 20 heteroarylamino carbonyl or a combination thereof, with the proviso that X and Y
 may optionally be additionally substituted with X¹¹ or X¹²;

X¹¹ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl,
 heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or
 heteroarylalkyl, with the proviso that X¹¹ may be additionally optionally substituted
 25 with X¹²;

X¹² is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro, with the proviso that said alkyl, alkoxy, and
 5 aryl may be additionally optionally substituted with moieties independently selected from X¹²;

W may be present or absent, and if W is present, W is selected from C=O, C=S, or SO₂;

Q may be present or absent, and when Q is present, Q is CH, N, P, (CH₂)_p,
 10 (CHR)_p, (CRR')_p, O, RNR, S, or SO₂; and when Q is absent, M is also absent, A is directly linked to X;

A is O, CH₂, (CHR)_p, (CHR-CHR')_p, (CRR')_p, NR, S, SO₂ or a bond;

U is selected from O, N, or CH;

E is CH, N or CR, or a double bond towards A, L or G;

15 G may be present or absent, and when G is present, G is (CH₂)_p, (CHR)_p, or (CRR')_p; and when G is absent, J is present and E is directly connected to the carbon atom where G was connected to;

J may be absent or present, and when J is present, J is (CH₂)_p, (CHR)_p, or (CRR')_p, SO₂, NH, NR or O; and when J is absent, G is present and L is directly
 20 linked to nitrogen;

L may be present or absent, and when L is present, L is CH, CR, O, S or NR; and when L is absent, then M may be absent or present, and if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

25 M may be present or absent, and when M is present, M is O, NR, S, SO₂, (CH₂)_p, (CHR)_p, (CHR-CHR')_p, or (CRR')_p;
 p is a number from 0 to 6;

R and R' are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3-C8 cycloalkyl; C3-C8 heterocycloalkyl, alkoxy,
 30 aryloxy, alkylthio, arylthio, amino, amido, cyano, nitro; (cycloalkyl)-alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally substituted, with said term "substituted" referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, cyano, nitro, sulfonamido; and

5 P^{1a}, P^{1b}, P¹ and P³ are independently selected from:

H, C1-C10 straight or branched chain alkyl, C2-C10 straight or branched chain alkenyl, and C3-C8 cycloalkyl, C3-C8 heterocyclic; (cycloalkyl)alkyl or

10 (heterocyclyl)alkyl, wherein said cycloalkyl is made up of 3 to 8 carbon atoms, and zero to 6 oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of 1 to 6 carbon atoms;

aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein said alkyl is of 1 to 6 carbon atoms;

15 wherein said alkyl, alkenyl, cycloalkyl, heterocyclyl; (cycloalkyl)alkyl and (heterocyclyl)alkyl moieties may be optionally substituted with Rⁿ, and further wherein said P^{1a} and P^{1b} may optionally be joined to each other to form a spirocyclic or spiroheterocyclic ring, with said spirocyclic or spiroheterocyclic ring containing zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and may be

20 additionally optionally substituted with Rⁿ;

Rⁿ is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy,

25 and aryl may be additionally optionally substituted with moieties independently selected from Rⁿ;

Z is O, NH or NR^m;

R^m is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or

30 heteroarylalkyl moiety, with the proviso that R^m may be additionally optionally substituted with Rⁿ;

Ar¹ and Ar² are independently selected from phenyl; 2-pyridyl, 3-pyridyl, 4-pyridyl or their corresponding N-oxides; 2-thiophenyl; 3-thiophenyl; 2-furanyl; 3-furanyl; 2-pyrrolyl; 3-pyrrolyl; 2-imidazolyl; 3(4)-imidazolyl; 3-(1,2,4-triazolyl); 5-tetrazolyl; 2-thiazolyl; 4-thiazolyl; 2-oxazolyl; or 4-oxazolyl; either or both of which may be
5 optionally substituted with R¹;

R¹ is H, halogen, cyano, nitro, CF₃, Si(alkyl)₃, straight-chain or branched lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl, hydroxy, alkoxy, aryloxy, alkoxycarbonyloxy, (alkylamino)carbonyloxy, mercapto, alkylthio, arylthio, alkylsulfinyl, heterocyclisulfinyl, arylsulfinyl,
10 heteroarylsulfinyl, alkylsulfonyl, heterocyclisulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylaminocarbonyl, arylaminocarbonyl, amino, alkylamino, arylamino, alkylsulfonamide, arylsulfonamide, alkoxycarbonbylamino, alkylureido, or arylureido;

15 P⁴ is H, linear or branched alkyl, arylalkyl or aryl; and

R² is H, cyano, CF₃, straight-chain or branched lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylsulfonyl, arylsulfonyl, carboxy, alkoxycarbonyl, aryloxy carbonyl, alkylaminocarbonyl, (allylamino)carbonyl, or arylaminocarbonyl.

20 Suitably, R² is selected from the group consisting of H, alkyl, alkenyl, alkoxycarbonyl, or (allylamino) carbonyl and preferably wherein R² is H, U is N and P⁴ is H.

Advantageously, Ar¹ and Ar² are independently selected from the group consisting of phenyl, 2-thiophenyl, 2-furanyl, 3-furanyl, 3(4)-imidazolyl, 3-(1,2,4-triazolyl), 5-tetrazolyl, or 2-thiazolyl, preferably Ar² is phenyl and Ar¹ is selected
25 from the group consisting of 3-(1,2,4-triazolyl), 5-tetrazolyl, or 2-thiazolyl and U is N and P⁴ is H.

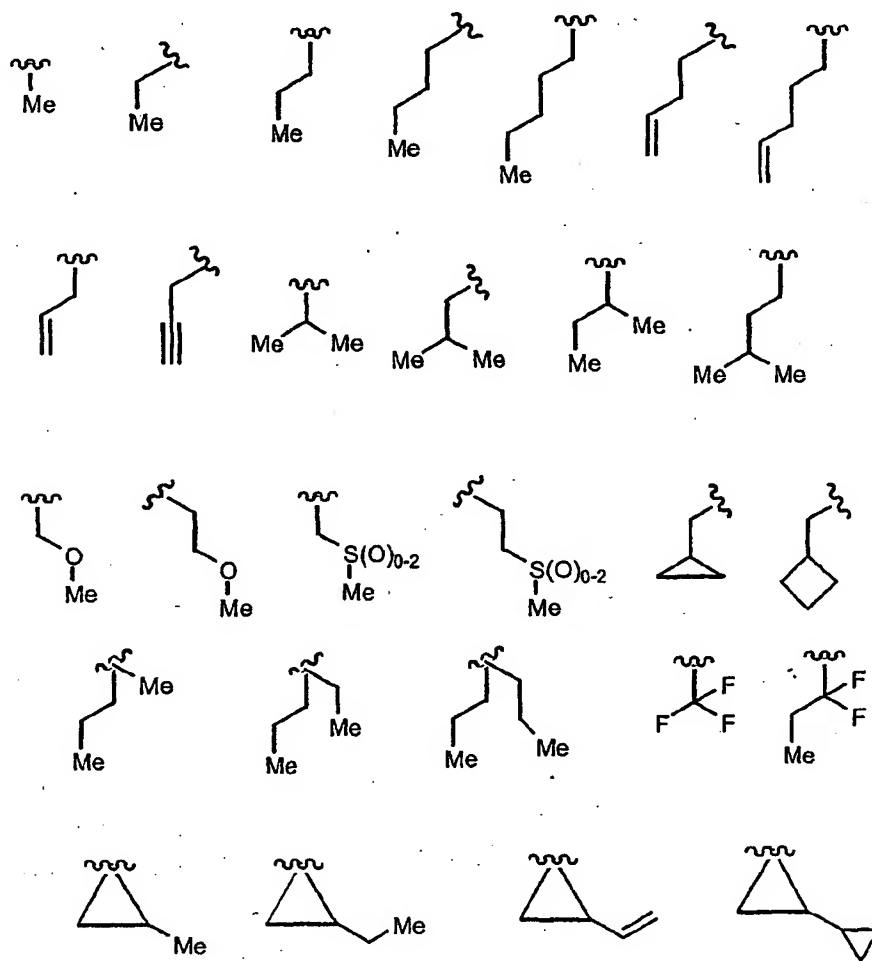
Suitably, R¹ is H, CF₃, CH₃, alkyl or alkenyl.

30 Usually, P¹ is either H or CH₃.

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Suitably, when P¹' is H then P¹' and the adjacent nitrogen and carbonyl moieties correspond to the residuum of a glycine unit.

Preferably, P^{1a} and P^{1b} are independently selected from the group consisting of the following moieties:

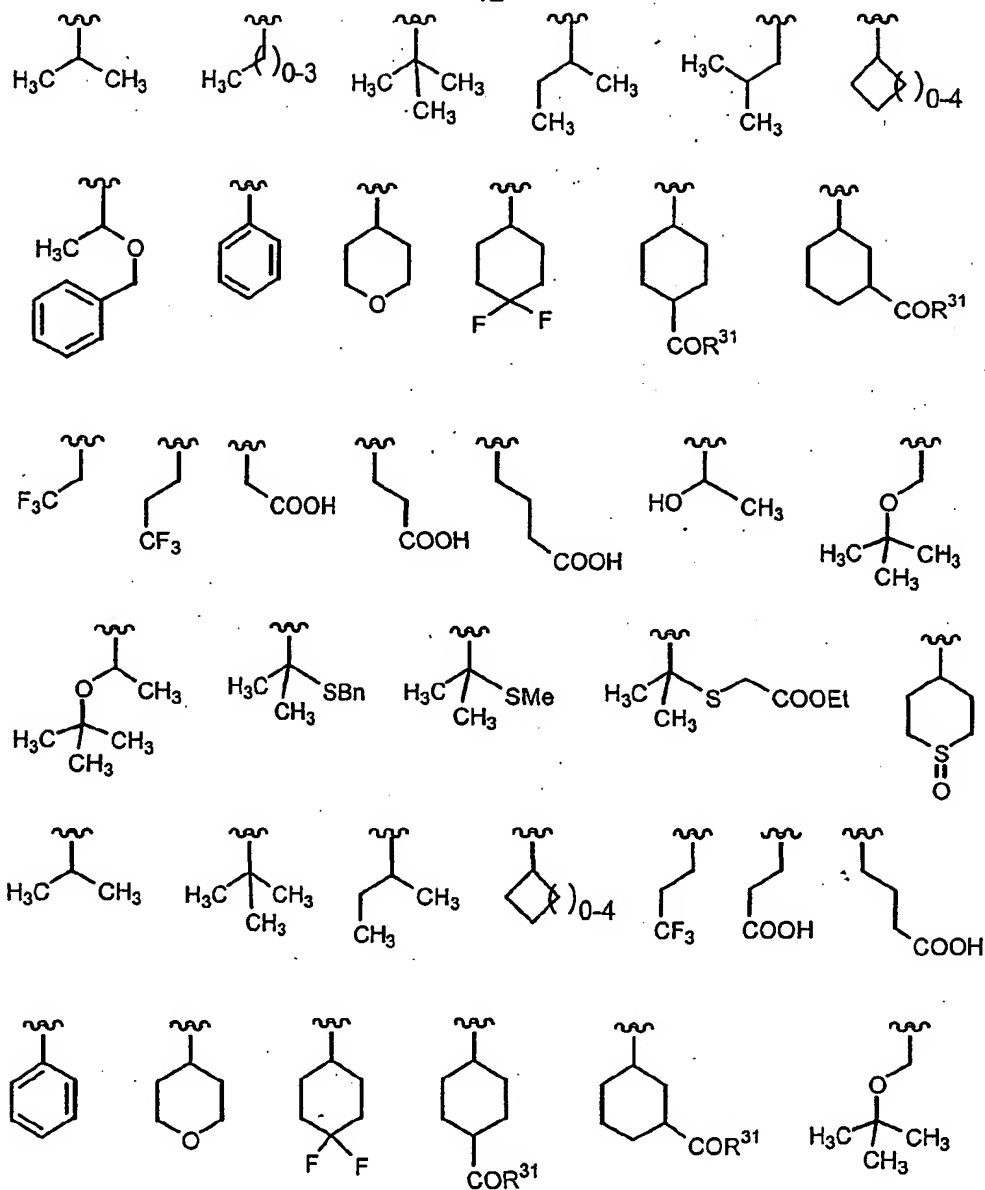


Advantageously, U is N and P⁴ is H and Z is NH.

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Suitably, P^3 is selected from the group consisting of:

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wherein $\text{R}^{31} = \text{OH}$ or O-alkyl.

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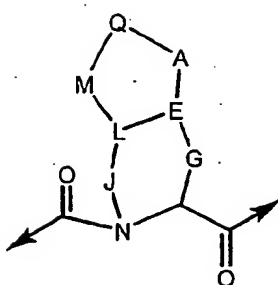
Suitably, P^4 is selected from the group consisting of H, tertiary butyl, isobutyl and phenyl substituents.

Suitably, Z is NH and U is N and P^3 is as set forth above.

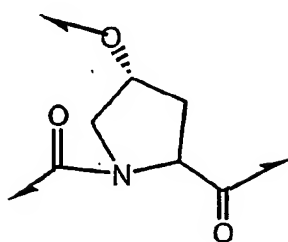
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In another suitable expression of Formula I, the moiety:

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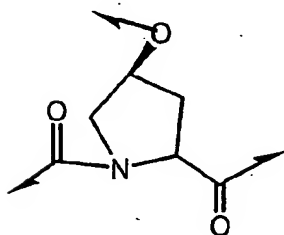


is



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or

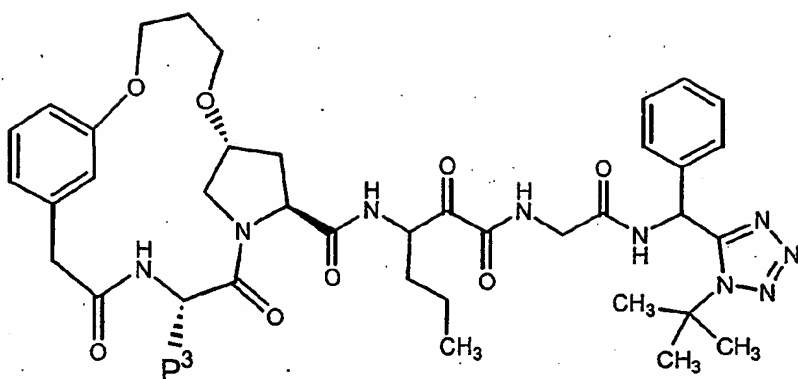


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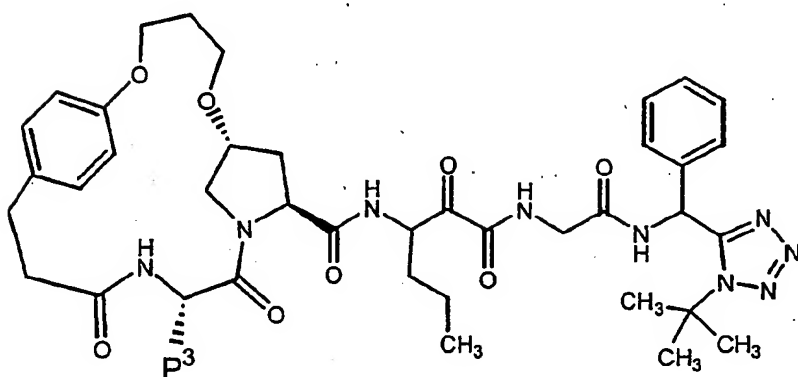
Suitably, Z is NH and U is N.

The compound of Formula I, wherein said compound is selected from the group consisting of compounds having the structural formulae:

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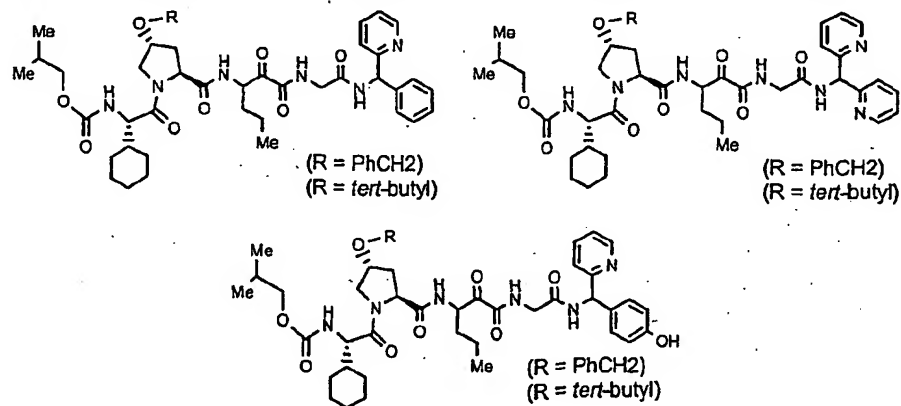


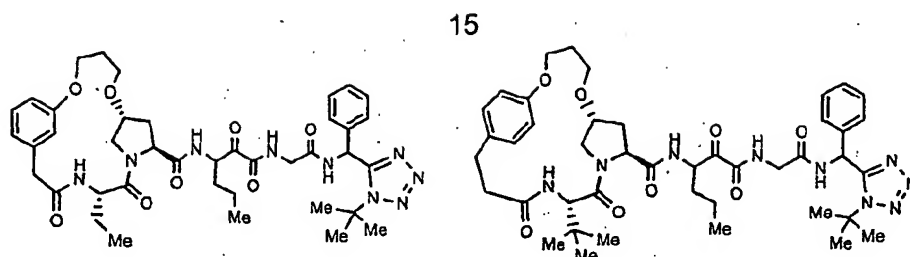
or



5 wherein P³ is an isopropyl, tertiary butyl, cyclopentyl, or cyclohexyl moiety.

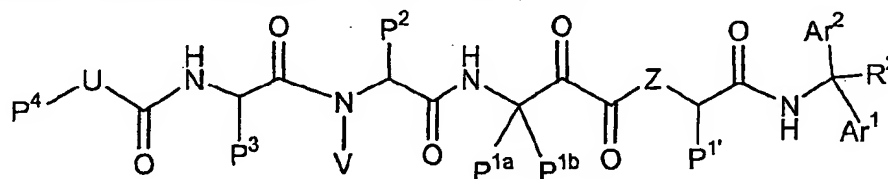
A preferred compound of Formula I exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said
10 compound being selected from the compounds of structures listed below:





In one embodiment, the present invention discloses compounds of Formula I as inhibitors of HCV protease, especially the HCV NS3/NS4a serine protease, or a pharmaceutically acceptable derivative thereof, where the various definitions are given above.

In another embodiment, the present invention discloses compounds including enantiomers, stereoisomers, rotomers and tautomers of said compound, and pharmaceutically acceptable salts, solvates or derivatives thereof, with said compound having the general structure shown in Formula II:



Formula II

wherein:

P^{1a} , P^{1b} , $P^{1'}$, P^2 , and P^3 are independently:

- 15 H, C1-C10 straight or branched chain alkyl, C2-C10 straight or branched chain alkenyl, and C3-C8 cycloalkyl, C3-C8 heterocyclic; (cycloalkyl)alkyl or (heterocyclyl)alkyl, wherein said cycloalkyl is made up of 3 to 8 carbon atoms, and zero to 6 oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of 1 to 6 carbon atoms;
- 20 aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein said alkyl is of 1 to 6 carbon atoms;
- wherein said alkyl, alkenyl, cycloalkyl, heterocyclyl; (cycloalkyl)alkyl and (heterocyclyl)alkyl moieties may be optionally substituted with R'' , and further wherein said P^{1a} and P^{1b} may optionally be joined to each other to form a
- 25 spirocyclic or spiroheterocyclic ring, with said spirocyclic or spiroheterocyclic ring

containing zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and may be additionally optionally substituted with Rⁿ;

Rⁿ is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from Rⁿ;

Z is O, NH or NR^m;

- 10 R^m is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that R^m may be additionally optionally substituted with Rⁿ;

- Ar¹ and Ar² are independently selected from phenyl; 2-pyridyl, 3-pyridyl, 4-pyridyl or their corresponding N-oxides; 2-thiophenyl; 3-thiophenyl; 2-furanyl; 3-furanyl; 2-pyrrolyl; 3-pyrrolyl; 2-imidazolyl; 3(4)-imidazolyl; 3-(1,2,4-triazolyl); 5-tetrazolyl; 2-thiazolyl; 4-thiazolyl; 2-oxazolyl; or 4-oxazolyl; either or both of which may be optionally substituted with R¹;

- R¹ is H, halogen, cyano, nitro, CF₃, Si(alkyl)₃, straight-chain or branched lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl, hydroxy, alkoxy, aryloxy, alkoxycarbonyloxy, (alkylamino)carbonyloxy, mercapto, alkylthio, arylthio, alkylsulfinyl, heterocyclisulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylsulfonyl, heterocyclisulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkyaminocarbonyl, arylaminocarbonyl, amino, alkylamino, arylamino, alkylsulfonamide, arylsulfonamide, alkoxycarbonbylamino, alkylureido, or arylureido;

P⁴ is H, linear or branched alkyl, arylalkyl or aryl;

- R² is H, cyano, CF₃, straight-chain or branched lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylsulfonyl, arylsulfonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, alkyaminocarbonyl, or arylaminocarbonyl;

17

U is O, NH, CH₂ or CHRⁿ; and

V is H, methyl, or lower alkyl.

In a suitable formulation in Formula II, R^{2'} is selected from the group
5 consisting of H, alkyl, alkenyl, alkoxy carbonyl, or (allylamino) carbonyl.

Advantageously in Formula II, Ar¹ and Ar² are independently selected from
the group consisting of phenyl, 2-thiophenyl, 2-furanyl, 3-furanyl, 3(4)-imidazolyl, 3-
(1,2,4-triazolyl), 5-tetrazolyl, or 2-thiazolyl.

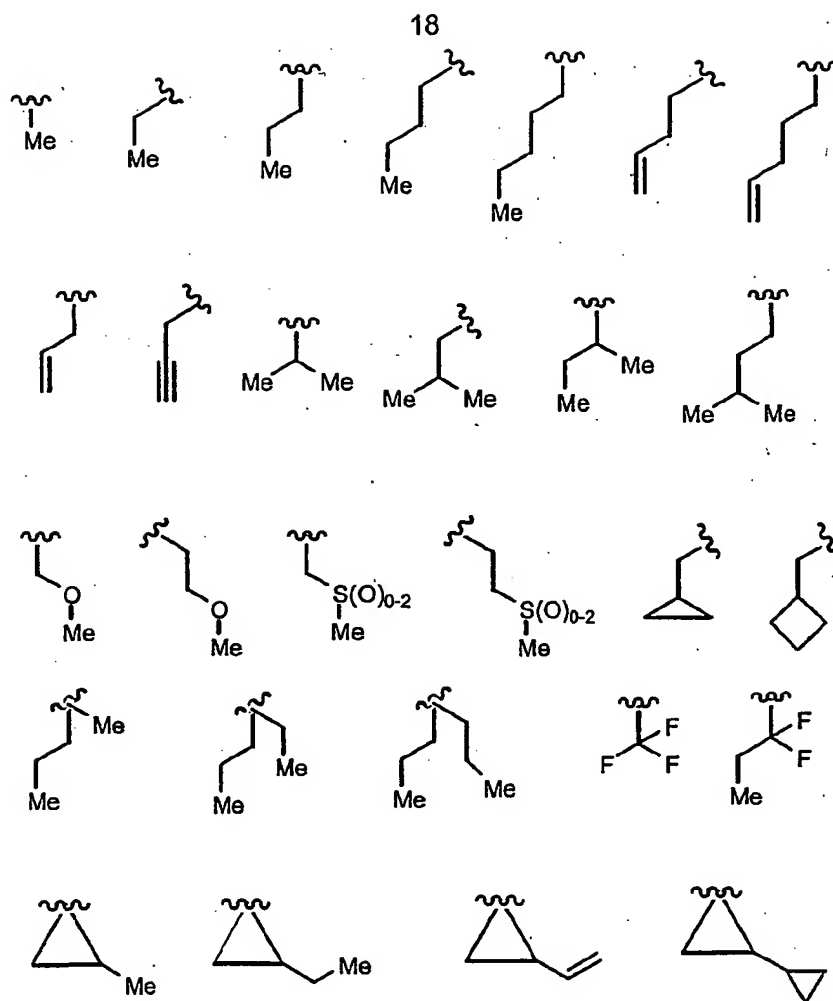
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Preferably, Ar² is phenyl and Ar¹ is selected from the group consisting of 3-
(1,2,4-triazolyl), 5-tetrazolyl, or 2-thiazolyl.

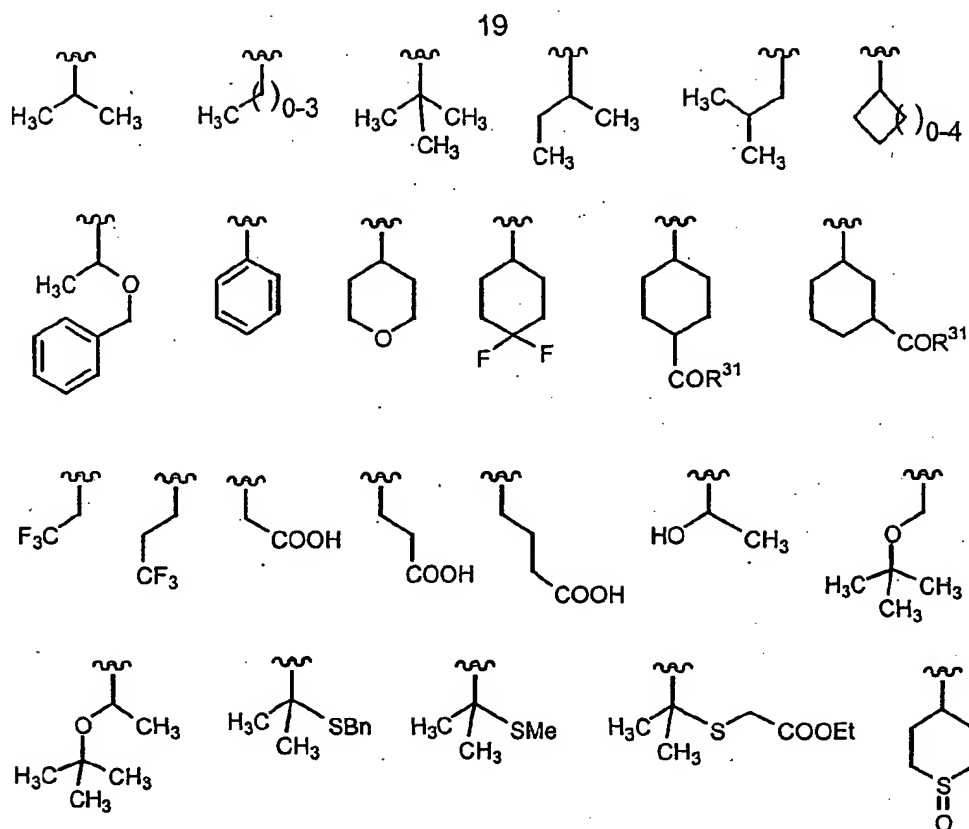
Suitably in Formula II, R¹ is H, CF₃, CH₃, alkyl or alkenyl and P^{1'} is either H
15 or CH₃.

Advantageously, P^{1'} is H such that P^{1'} and the adjacent nitrogen and
carbonyl moieties correspond to the residuum of glycine unit.

20 Suitably in Formula II, P^{1a} and P^{1b} is selected from the group consisting of
the following moieties:

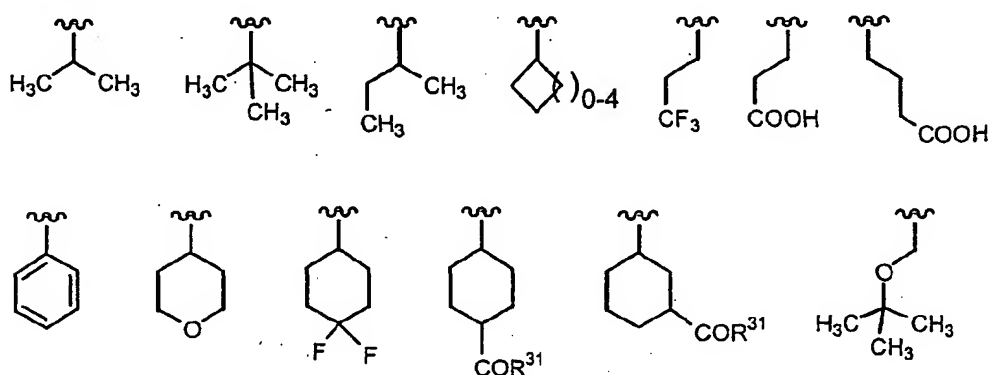


Advantageously in Formula II, P^3 is selected from the group consisting of:



wherein $R^{31} = \text{OH}$ or O-alkyl .

Preferably in Formula II, R^3 is selected from the group consisting of the following moieties:

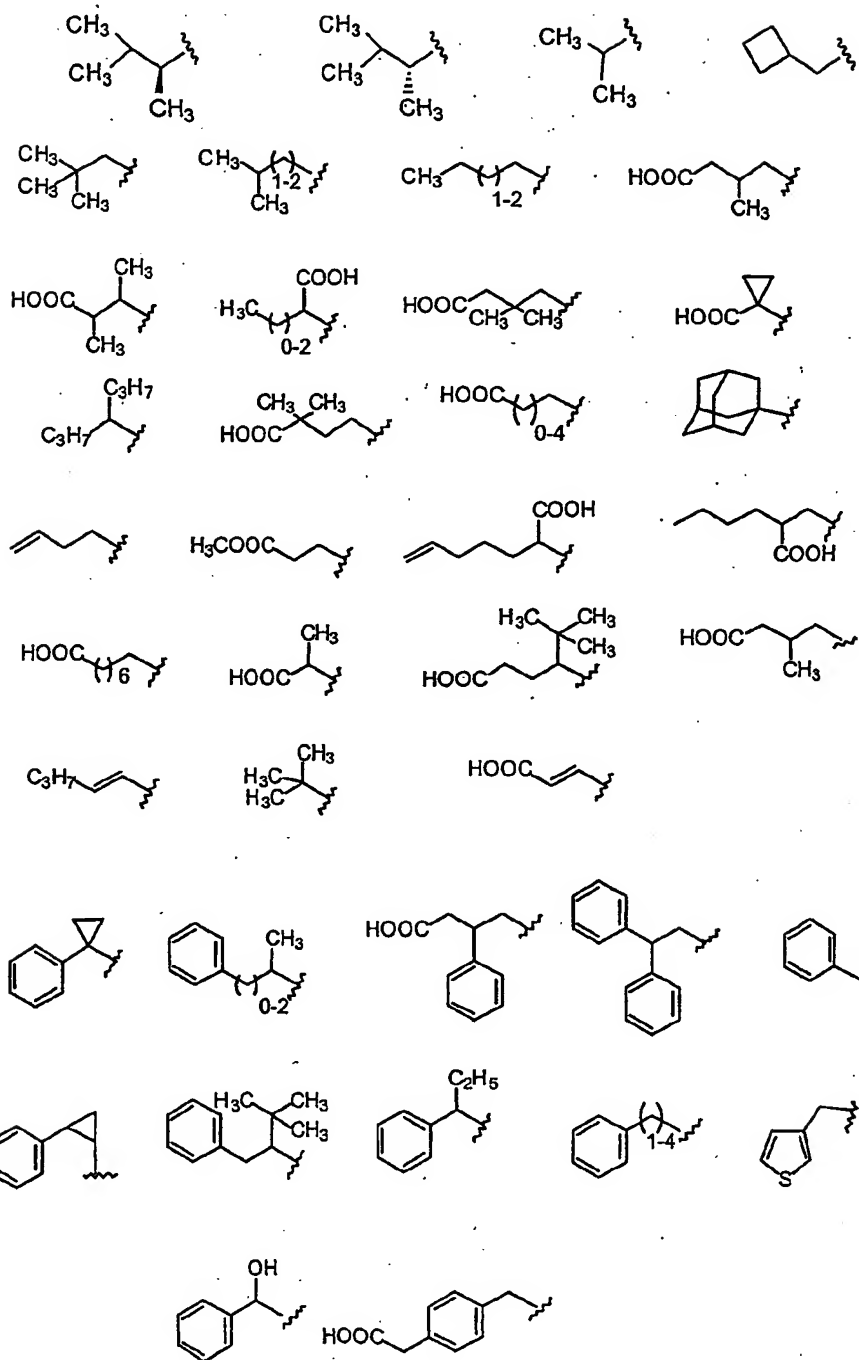


Suitably in Formula II, U is N and P^4 is alkyl or arylalkyl.

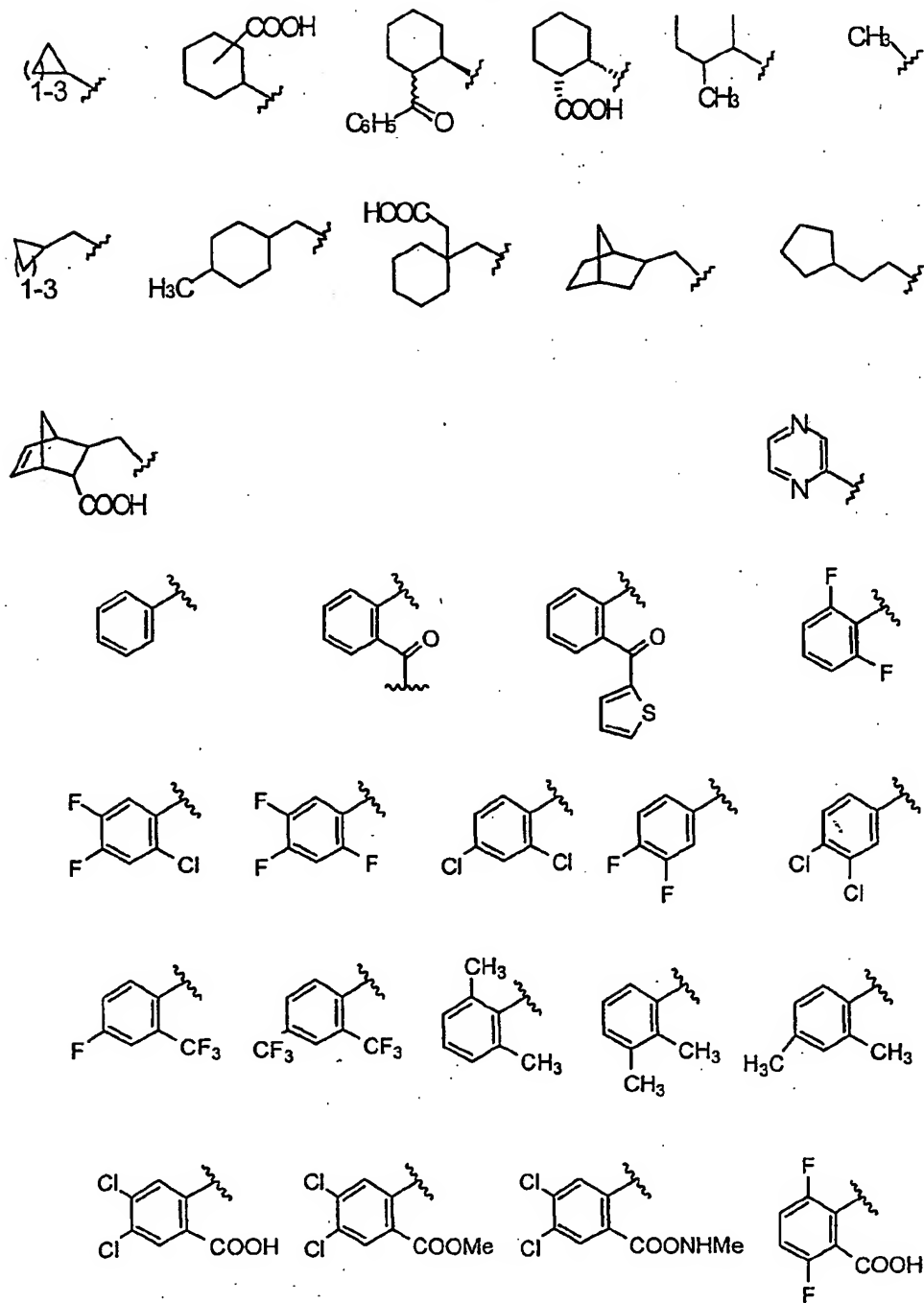
Preferably U is O or CH_2 .

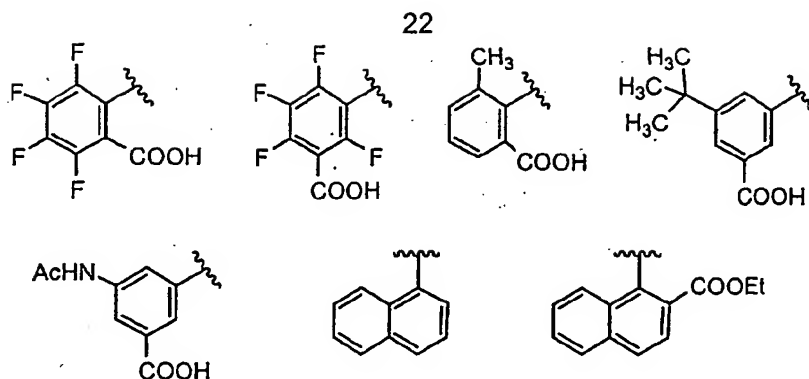
20

P⁴ is selected from the following moieties:



21

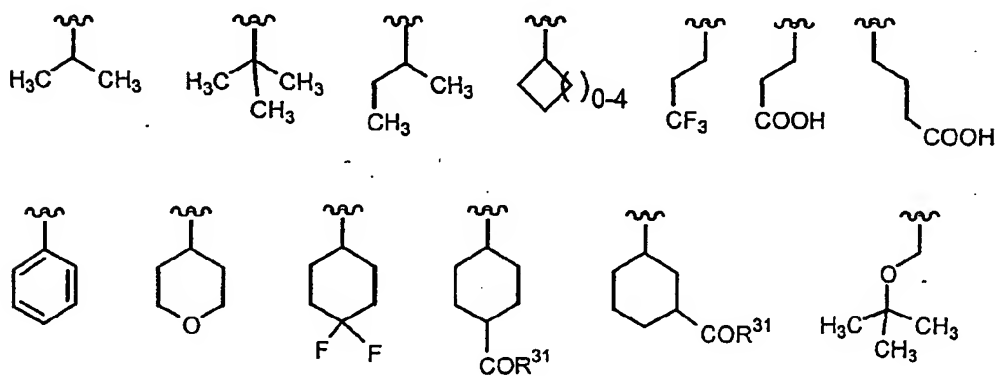




Suitably in Formula II, U is CH₂ and P⁴ is phenyl or U is O and P⁴ is selected from the group consisting of methyl, tertiary butyl, isobutyl, and 2,3-dimethylpropyl.

In Formula II, P² and P³ are independently selected from the group consisting of: H, linear alkyl, branched alkyl, or arylalkyl, such that P² or P³ and the adjacent nitrogen and carbonyl moieties thereto correspond to the residuum of an alpha amino acid.

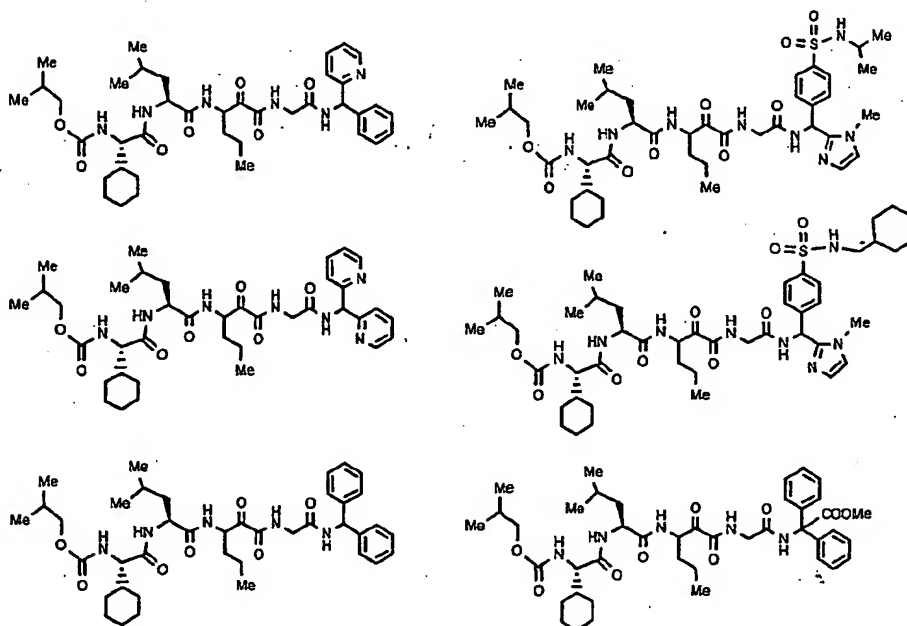
Preferably, P³ is selected from the following moieties:



Suitably, P³ is selected from the group consisting of isopropyl tertiary butyl, isobutyl and cyclohexyl substituents.

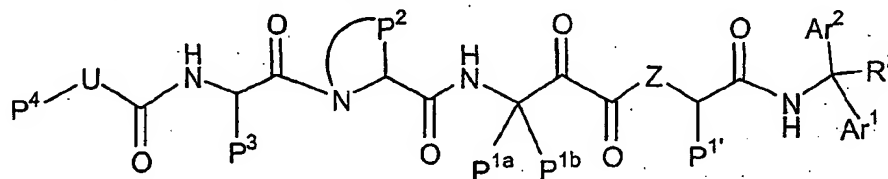
Advantageously, in Formula II, V is H.

A preferred compound of Formula II exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said
 5 compound being selected from the compounds of structures listed below:



10

In another embodiment, the present invention discloses compounds of Formula III as inhibitors of HCV protease, especially the HCV NS3/NS4a serine protease, or a pharmaceutically acceptable derivative thereof. The compound of Formula III has the following structure:



15

Formula III

wherein:

P^{1a}, P^{1b}, P^{1'}, P², and P³ are independently selected from:

H, C1-C10 straight or branched chain alkyl, C2-C10 straight or branched chain alkenyl; and C3-C8 cycloalkyl, C3-C8 heterocyclic; (cycloalkyl)alkyl or
5 (heterocyclyl)alkyl, wherein said cycloalkyl is made up of 3 to 8 carbon atoms, and zero to 6 oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of 1 to 6 carbon atoms;

aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein said alkyl is of 1 to 6 carbon atoms;

10 wherein said alkyl, alkenyl, cycloalkyl, heterocyclyl; (cycloalkyl)alkyl and (heterocyclyl)alkyl moieties may be optionally substituted with R", and further wherein said P^{1a} and P^{1b} may optionally be joined to each other to form a spirocyclic or spiroheterocyclic ring, with said spirocyclic or spiroheterocyclic ring containing zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and may be
15 additionally optionally substituted with R";

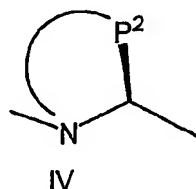
R" is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy, and aryl
20 may be additionally optionally substituted with moieties independently selected from R";

Z is O, NH or NR^{'''};

R^{'''} is alkyl, alkenyl, alkynyl; cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or
25 heteroarylalkyl moiety, with the proviso that R^{'''} may be additionally optionally substituted with R";

Ar¹ and Ar² are independently selected from phenyl; 2-pyridyl, 3-pyridyl, 4-pyridyl or their corresponding N-oxides; 2-thiophenyl; 3-thiophenyl; 2-furanyl; 3-furanyl; 2-pyrrolyl; 3-pyrrolyl; 2-imidazolyl; 3(4)-imidazolyl; 3-(1,2,4-triazolyl); 5-tetrazolyl; 2-thiazolyl; 4-thiazolyl; 2-oxazolyl; or 4-oxazolyl; either or both of which may be
30 optionally substituted with R¹;

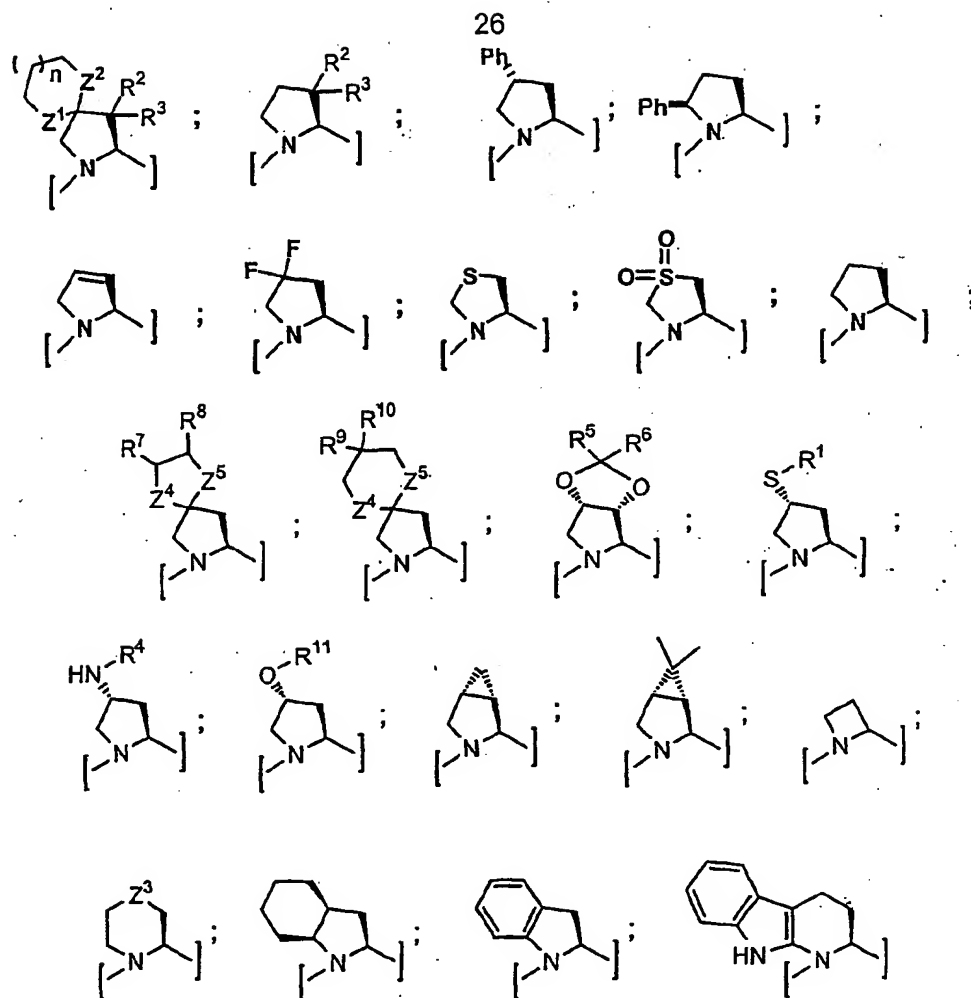
- R¹ is H, halogen, cyano, nitro, CF₃, Si(alkyl)₃, straight-chain or branched lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl, hydroxy, alkoxy, aryloxy, alkoxycarbonyloxy, (alkylamino)carbonyloxy, mercapto, alkylthio, arylthio, alkylsulfinyl, heterocyclisulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylsulfonyl, heterocyclisulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxy, heteroaryloxy, alkyaminocarbonyl, arylaminocarbonyl, amino, alkylamino, arylamino, alkylsulfonamido, arylsulfonamido, alkoxycarbonbylamino, alkylureido, or arylureido;
- P⁴ is H, linear or branched alkyl, arylalkyl or aryl;
- R² is H, cyano, CF₃, straight-chain or branched lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylsulfonyl, arylsulfonyl, carboxy, alkoxycarbonyl, aryloxy, alkyaminocarbonyl, or arylaminocarbonyl;
- U is O, NH, CH₂ or CHRⁿ;
- and



where moiety IV indicates a cyclic ring structure, with the proviso that said cyclic ring structure does not contain a carbonyl group as part of the cyclic ring.

Preferably moiety IV is a five- or six-membered ring.

Advantageously, the moiety IV forms a structural unit selected from the group consisting of:



wherein n = 0, 1, 2, or 3; and

R² = R³ = H; R² = C₁ to C₆ straight chainalkyl or cycloalkyl; R³ = H

R⁴ = COAlkyl (straight chain or cyclic, C₁ to C₆); COAryl; COOAlkyl; COOAryl

R⁵ = H; R⁶ = Alkyl (C₁ to C₃); R⁶ = H; R⁵ = Alkyl (C₁ to C₃)

5 R⁷ = H; R⁸ = Alkyl (C₁ to C₃), CH₂OH; R⁸ = H; R⁷ = Alkyl (C₁ to C₃), CH₂OH;

R⁹ = R¹⁰ = Alkyl (C₁ to C₃); R⁹ = H, R¹⁰ = Alkyl (C₁ to C₃), COOMe, COOH, CH₂OH;

R¹⁰ = H, R⁹ = Alkyl (C₁ to C₃), COOMe, COOH, CH₂OH;

10 R¹¹ = Alkyl (C₁ to C₆ straight chain, branched or cyclic), CH₂Aryl (may be substituted)

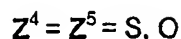
X¹ = H, Alkyl (C₁ to C₄, branched or straight chain); CH₂Aryl (substituted or unsubstituted)

15 Z¹ = Z² = S, O; Z¹ = S, Z² = O; Z¹ = O, Z² = S; Z¹ = CH₂, Z² = O; Z¹ = O, Z² = CH₂;

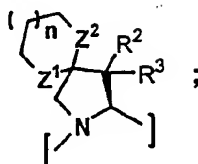
Z¹ = S, Z² = CH₂; Z¹ = CH₂, Z² = S

Z³ = CH₂, S, SO₂, NH, NR⁴

27



Advantageously, the cyclic ring moiety is



5

wherein Z^1 and Z^2 are S, R^2 and R^3 are H and $n=1$ or 2.

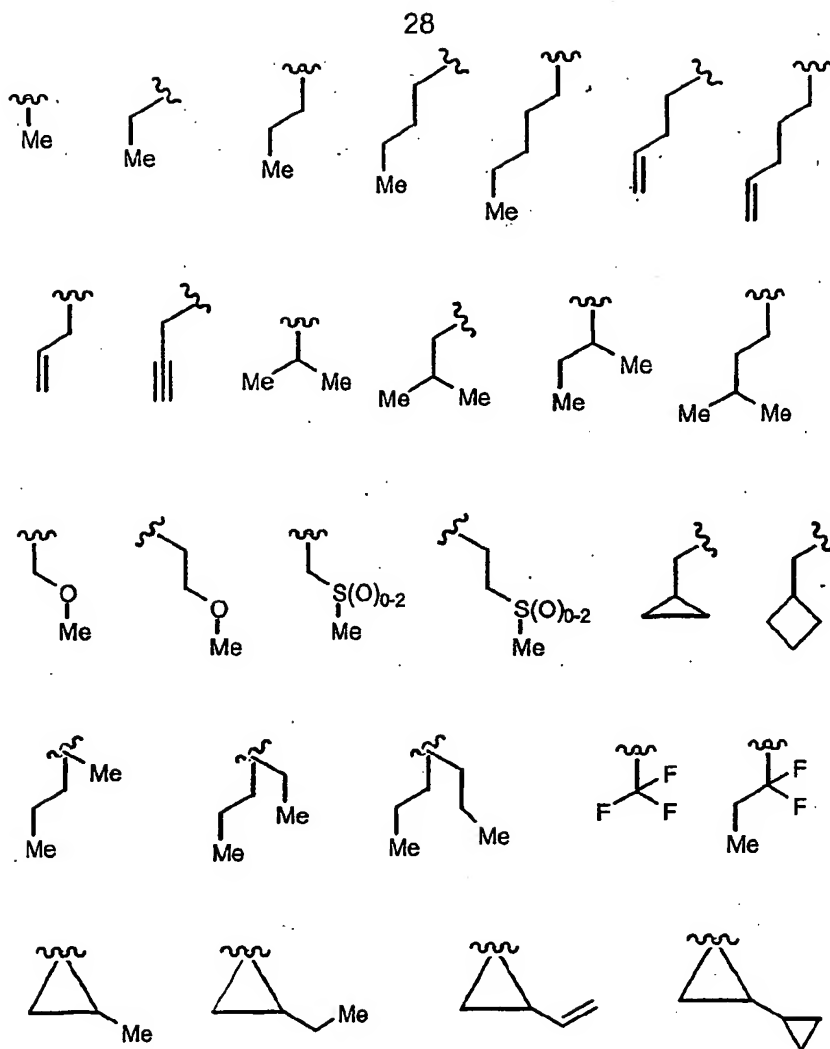
10 Suitably for the compound of Formula III, $R^{2'}$ is selected from the group consisting of H, alkyl, alkenyl, alkoxycarbonyl, or (allylamino) carbonyl and Ar^1 and Ar^2 are independently selected from the group consisting of phenyl, 2-thiophenyl, 2-furanyl, 3-furanyl, 3(4)-imidazolyl, 3-(1,2,4-triazolyl), 5-tetrazolyl, or 2-thiazolyl.

15 Advantageously, Ar^2 is phenyl and Ar^1 is selected from the group consisting of 3-(1,2,4-triazolyl), 5-tetrazolyl, or 2-thiazolyl.

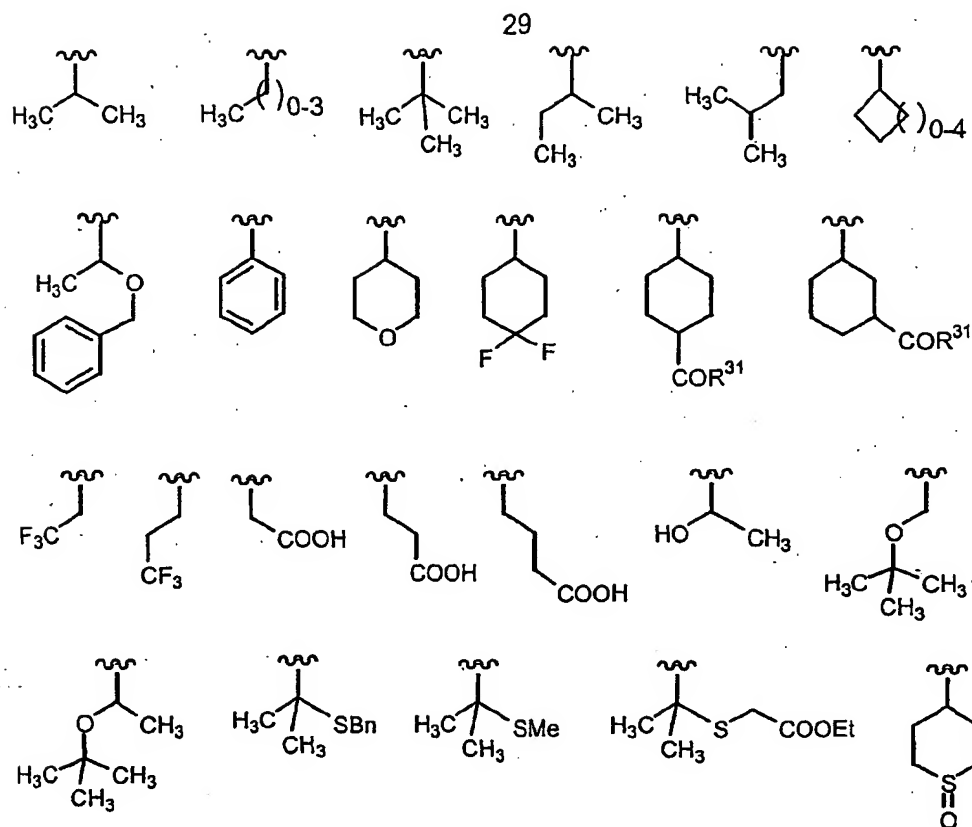
The compound of Formula III wherein in moiety IV, R^1 is H, CF_3 , CH_3 , alkyl or alkenyl and $P^{1'}$ is selected from the group consisting of H, F or CH_3 . In another
20 embodiment, $P^{1'}$ is H such that $P^{1'}$ and the adjacent nitrogen and carbonyl moieties correspond to the residuum of glycine unit.

The compound of Formula III, wherein P^{1a} and P^{1b} is selected from the group consisting of the following moieties:

25

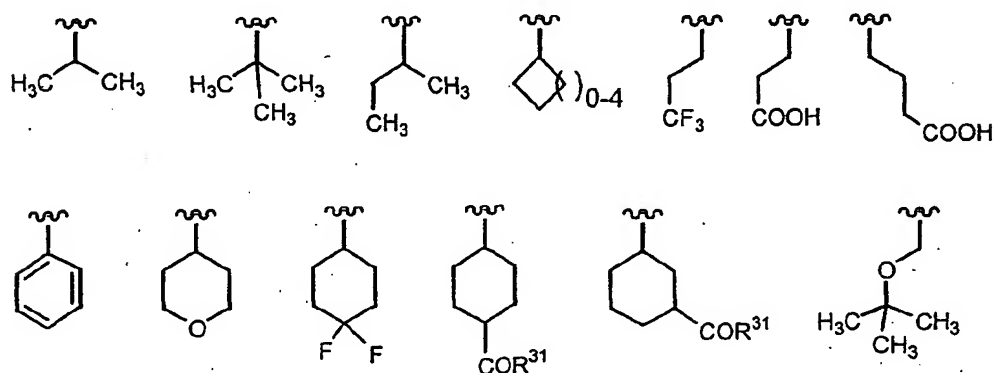


and P³ is selected from the group consisting of:



wherein $R^{31} = \text{OH}$ or O-alkyl.

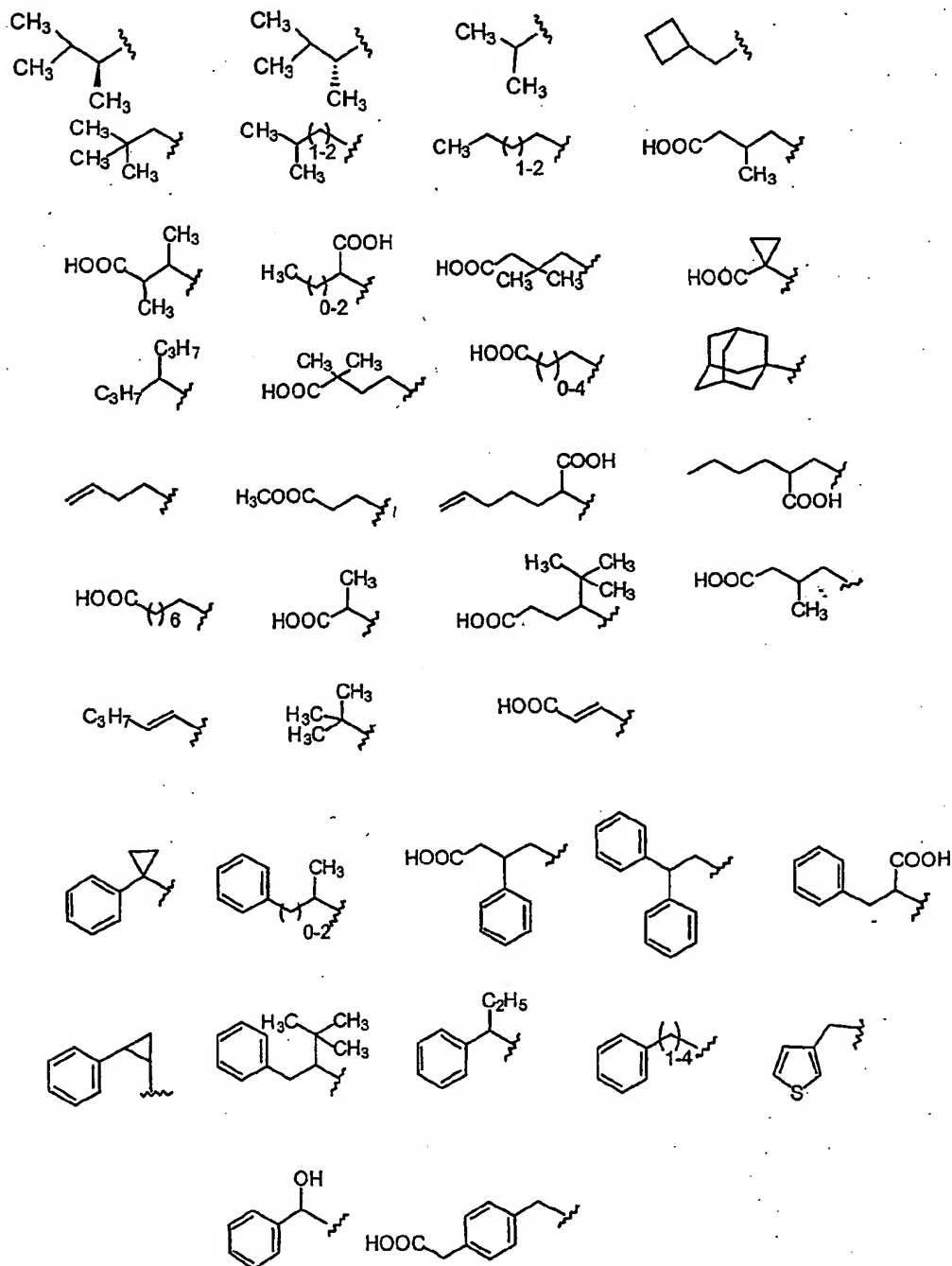
The compound of Formula III wherein moiety IV, R^3 is selected from the
 5 group consisting of the following moieties:



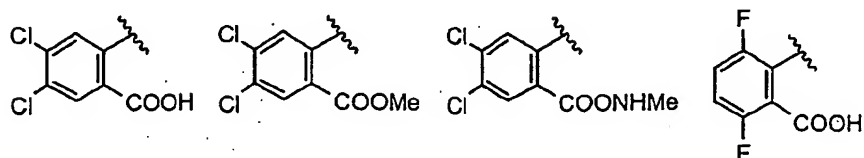
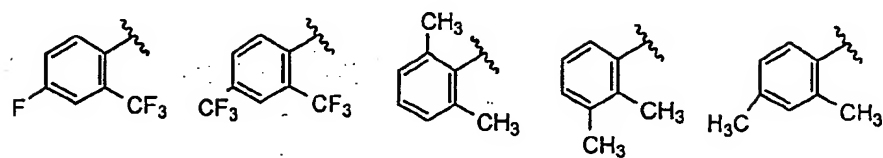
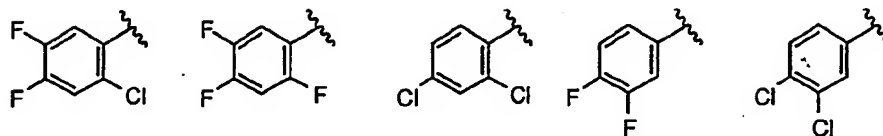
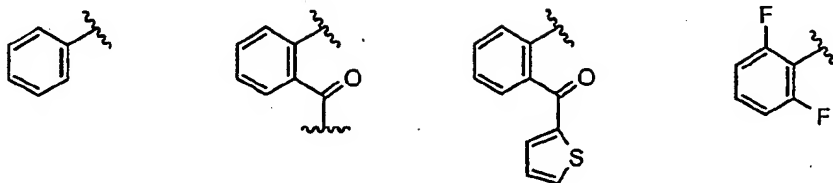
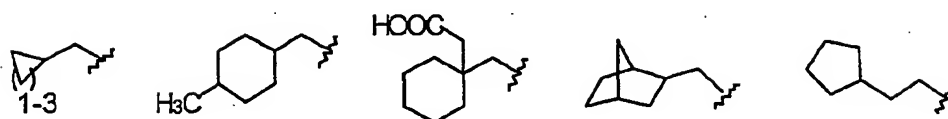
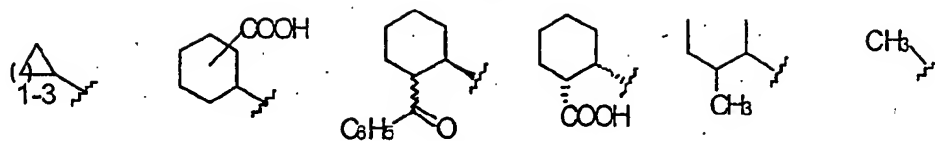
The compound of Formula III wherein moiety U is O or CH_2 .

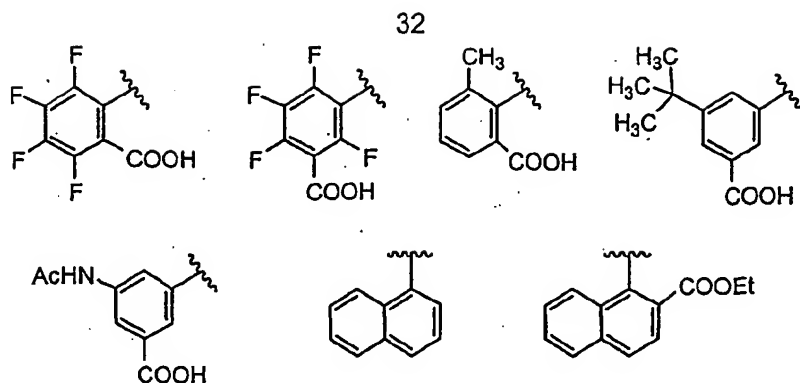
The compound of Formula III wherein in moiety IV, U is NH or O, and P⁴ is alkyl or arylalkyl.

Advantageously moiety IV of Formula III comprises P⁴ selected from the following moieties:



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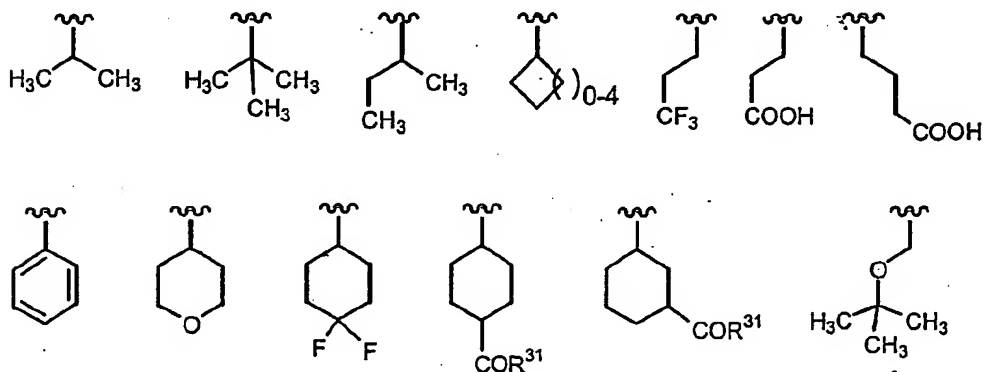




Advantageously in moiety IV, U is CH₂ and P⁴ is phenyl or U is O and P⁴ is selected from the group consisting of methyl, tertiary butyl, isobutyl, and 2,3-dimethylpropyl.

Suitably in moiety IV, P² and P³ are independently selected from the group consisting of: H, linear alkyl, branched alkyl, or arylalkyl, such that P² OR P³ and the adjacent nitrogen and carbonyl moieties thereto correspond to the residuum of an alpha amino acid.

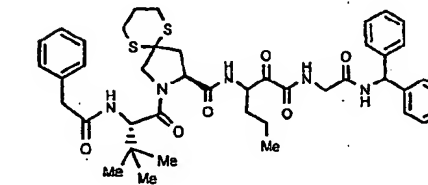
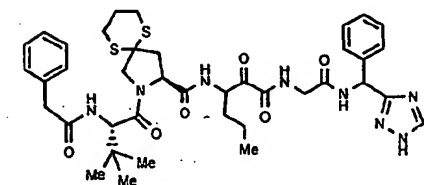
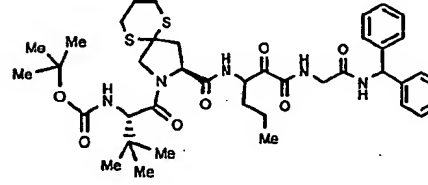
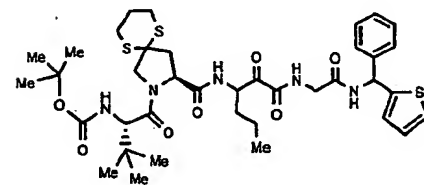
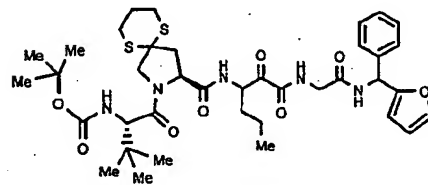
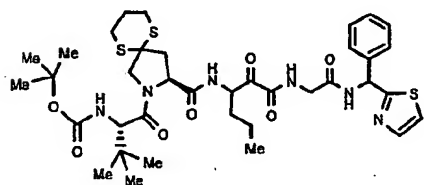
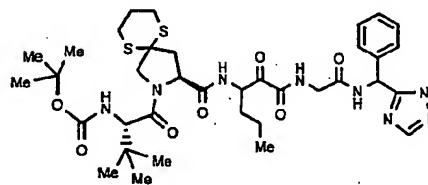
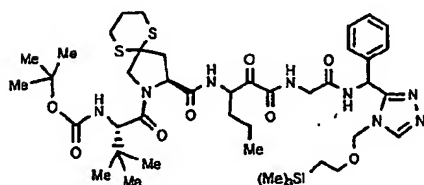
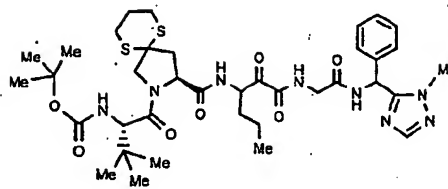
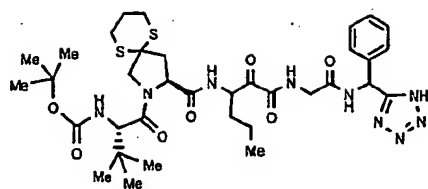
Advantageously, P³ is selected from the following moieties:



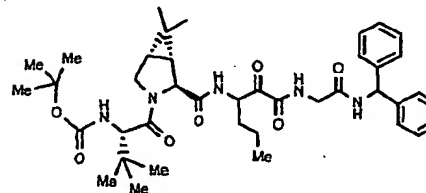
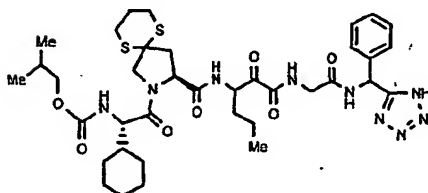
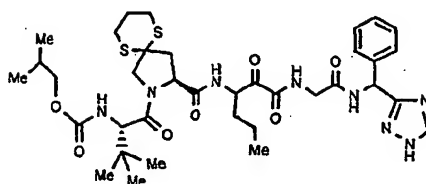
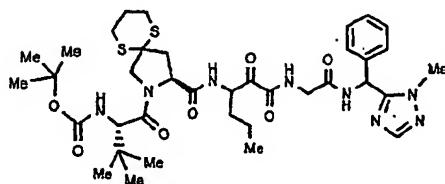
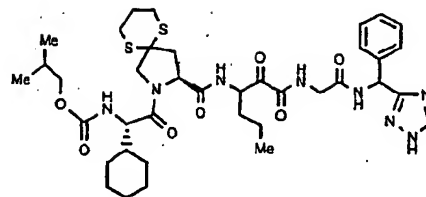
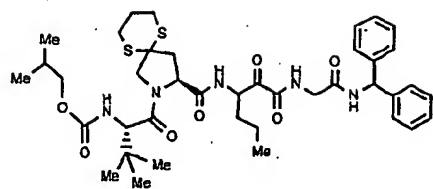
Preferably, P³ is selected from the group consisting of isopropyl, tertiary butyl, isobutyl and cyclohexyl substituents.

The compound according to Formula III, wherein said compound is selected from the group consisting of:

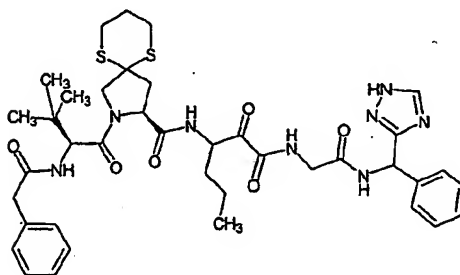
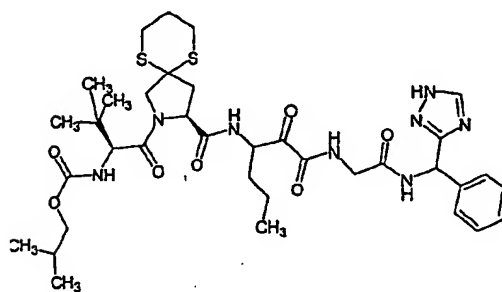
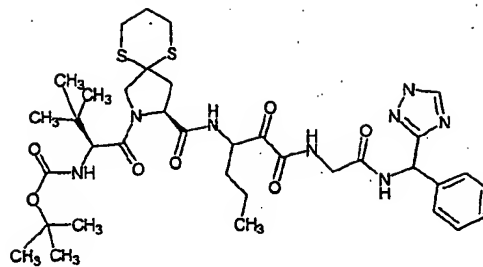
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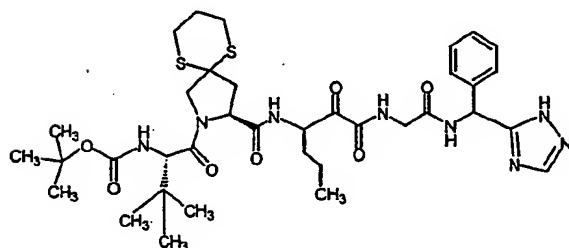
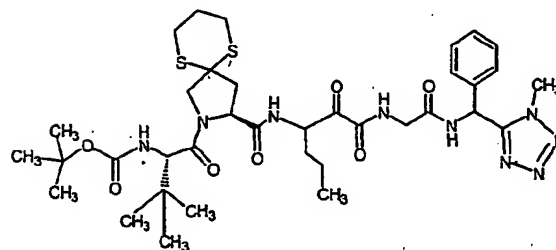
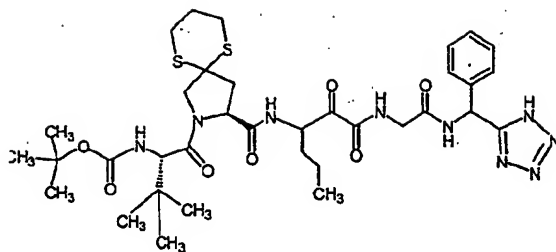
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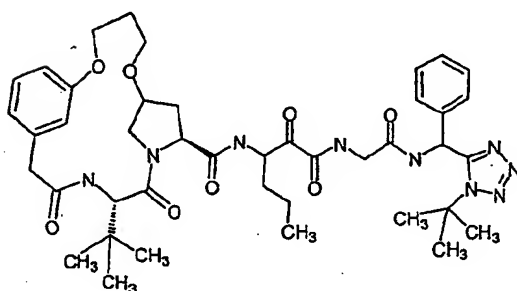
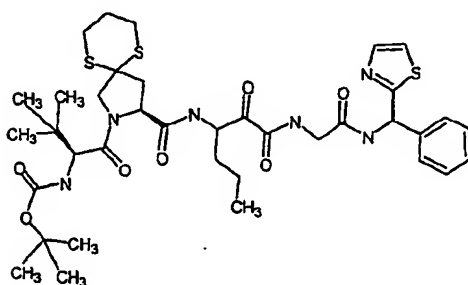
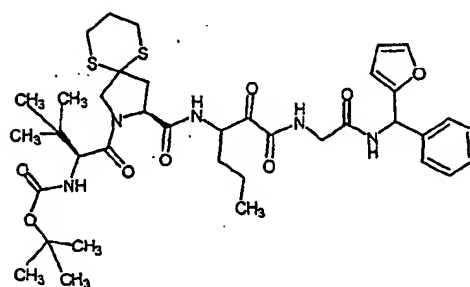
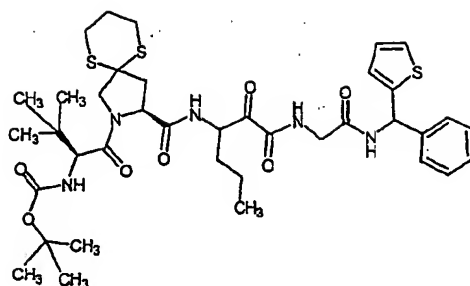
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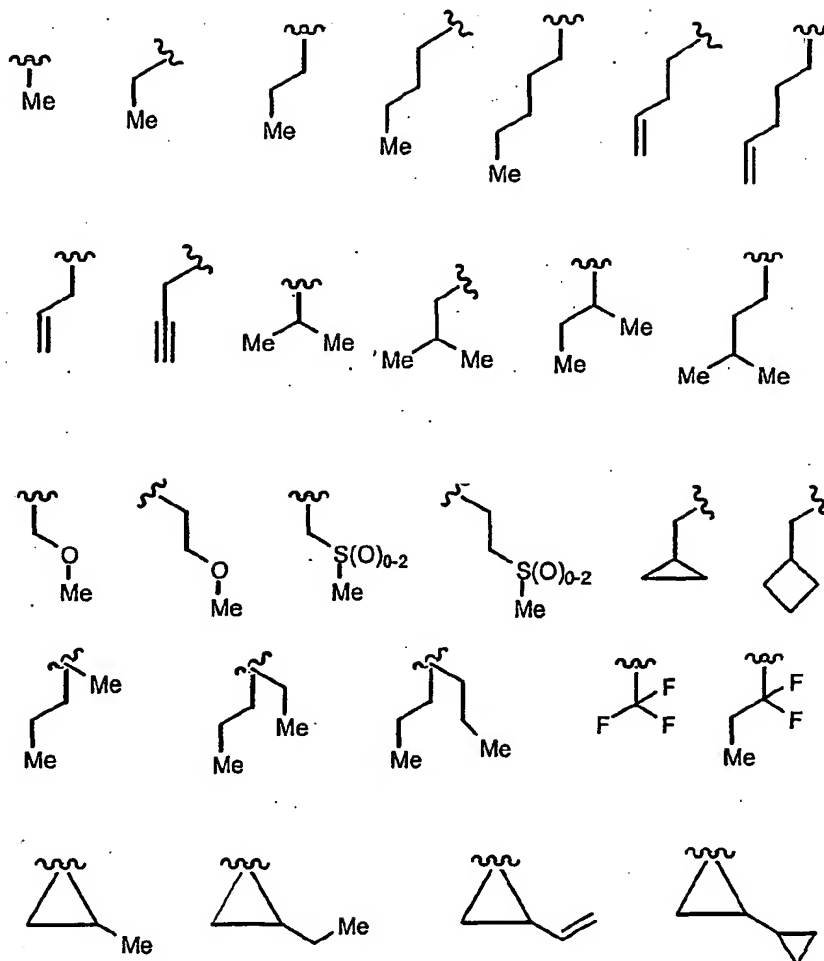
39



5 The following description of suitable moieties is applicable for
compounds of Formulas I, II and III:

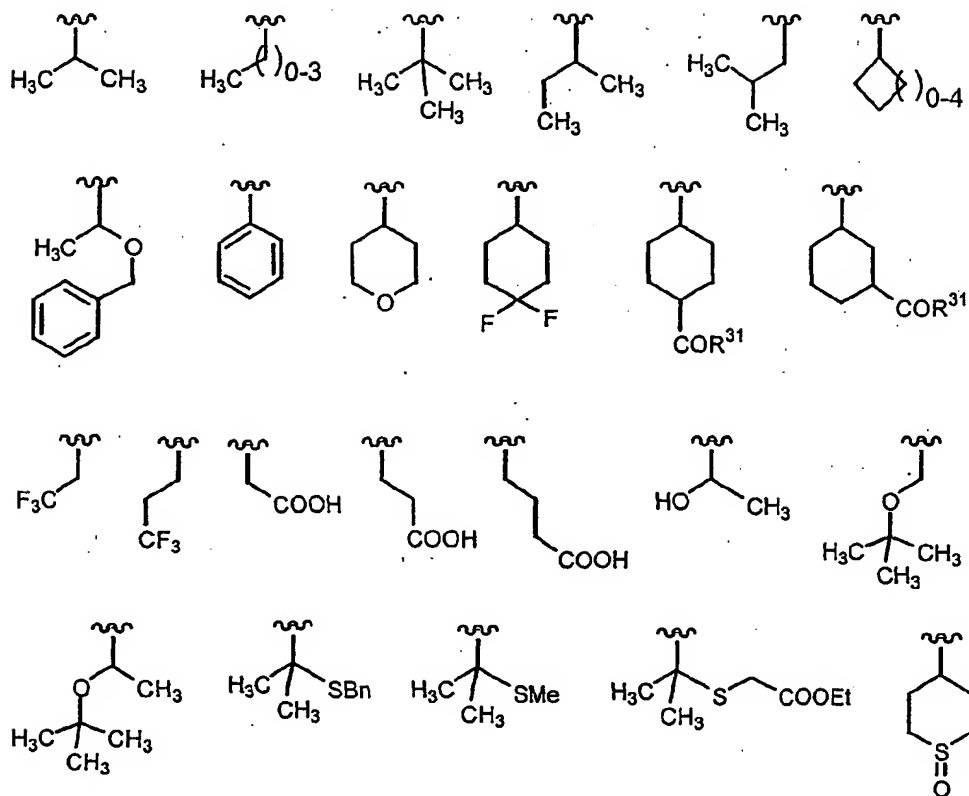
The following moieties are suitable P^1 moieties:

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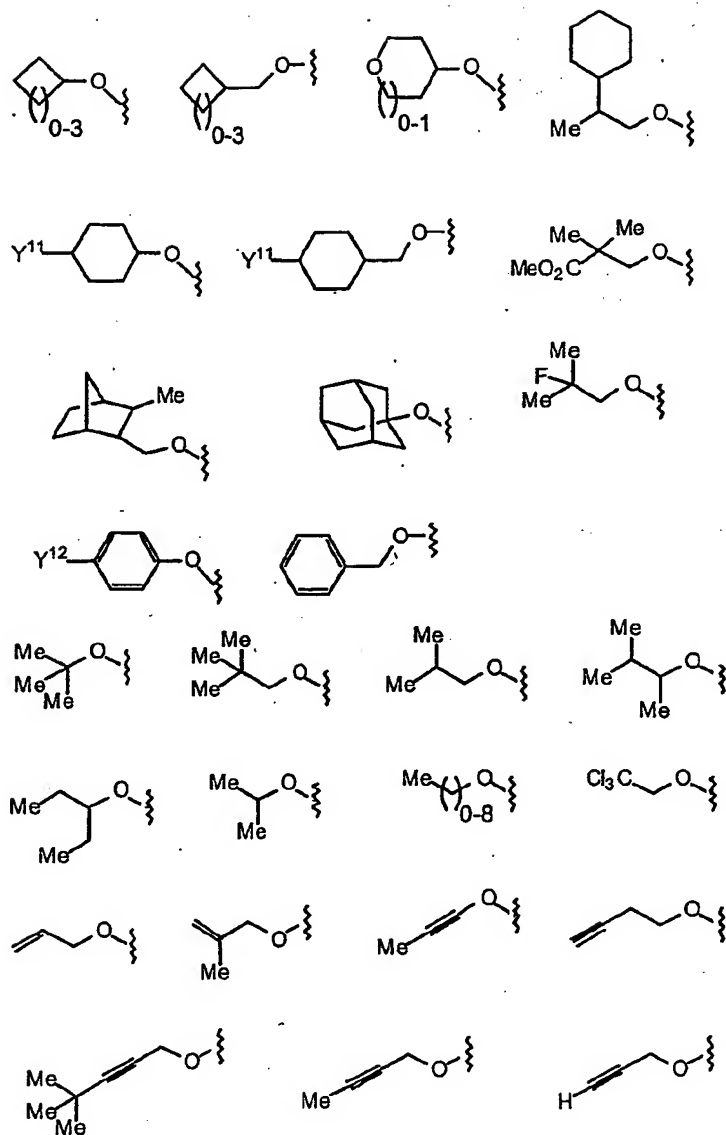
Also, the following moieties are suitable P^3 moieties:

41



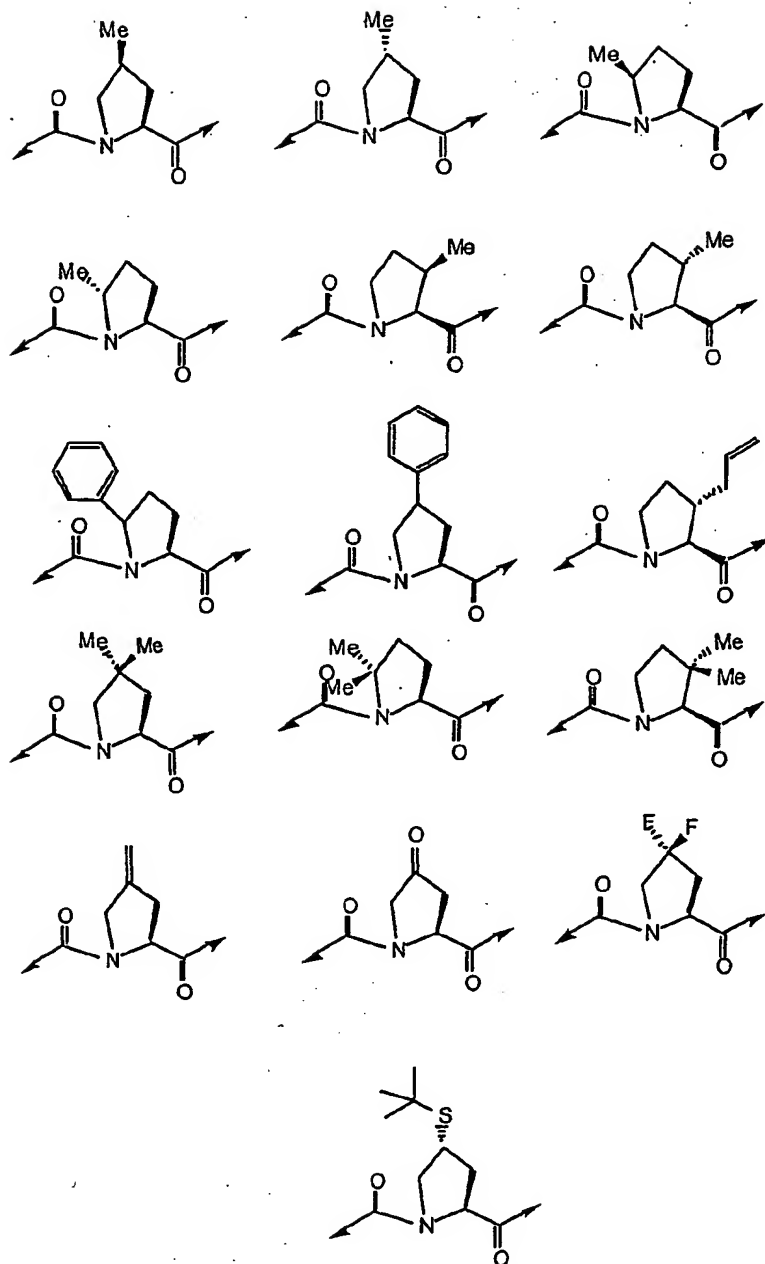
The following moieties are suitable Y moieties:

42



The following moieties are suitable V-P2 moieties:

43



Depending upon their structure, the compounds of the invention may form pharmaceutically acceptable salts with organic or inorganic acids, or organic or inorganic bases. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic,

salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. For formation of salts with bases, suitable bases are, for example, NaOH, KOH, NH_4OH , tetraalkylammonium hydroxide, and the like.

5 In another embodiment, this invention provides pharmaceutical compositions comprising the inventive peptides as an active ingredient. The pharmaceutical compositions generally additionally comprise a pharmaceutically acceptable carrier diluent, excipient or carrier (described below and collectively referred to herein as carrier materials). Because of
10 their HCV inhibitory activity, such pharmaceutical compositions possess utility in treating hepatitis C and related disorders.

In yet another embodiment, the present invention discloses methods for preparing pharmaceutical compositions comprising the inventive compounds as an active ingredient. In the pharmaceutical
15 compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups,
20 suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium
25 phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition. Suitable binders include starch, gelatin,
30 natural sugars, corn sweeteners, natural and synthetic gums such as

acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like. Sweetening and flavoring agents and preservatives may also be included where appropriate. Some of the terms noted above, namely disintegrants, diluents, lubricants, binders and the like, are discussed in more detail below.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e. HCV inhibitory activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injections or addition of sweeteners and pacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier such as inert compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides such as cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein by stirring or similar mixing.

The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions may take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

The quantity of the inventive active composition in a unit dose of preparation may be generally varied or adjusted from about 1.0 milligram to about 1,000 milligrams, preferably from about 1.0 to about 950 milligrams, more preferably from about 1.0 to about 500 milligrams, and typically from about 1 to about 250 milligrams, according to the particular application. The actual dosage employed may be varied depending upon the patient's age, sex, weight and severity of the condition being treated. Such techniques are well known to those skilled in the art.

Generally, the human oral dosage form containing the active ingredients can be administered 1 or 2 times per day. The amount and frequency of the administration will be regulated according to the judgment of the attending clinician. A generally recommended daily dosage regimen for oral administration may range from about 1.0 milligram to about 1,000 milligrams per day, in single or divided doses.

Some useful terms are described below:

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gel- refers to the active ingredients dispersed or solubilized in a hydrophillic semi-solid matrix.

Powder for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

Diluent - refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

Disintegrant - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline

celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binder - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d,l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition,

preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glident - material that prevents caking and improve the flow characteristics of granulations, so that flow is smooth and uniform.

- 5 Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

- 10 Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

- 15 Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

- 20 Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures. Conventional methods for making other forms for administration such as, for example, capsules, suppositories and the like are also well known.

- 25 Another embodiment of the invention discloses the use of the pharmaceutical compositions disclosed above for treatment of diseases such as, for example, hepatitis C and the like. The method comprises administering a therapeutically effective amount of the inventive pharmaceutical composition to a patient having such a disease or diseases and in need of such a treatment.

- 30 As stated earlier, the invention includes tautomers, rotamers, enantiomers and other stereoisomers of the compounds also. Thus, as

one skilled in the art appreciates, some of the inventive compounds may exist in suitable isomeric forms. Such variations are contemplated to be within the scope of the invention.

Another embodiment of the invention discloses a method of making
5 the compounds disclosed herein. The compounds may be prepared by several techniques known in the art. Representative illustrative procedures are outlined in the following reaction schemes. It is to be understood that while the following illustrative schemes describe the preparation of a few representative inventive compounds, suitable
10 substitution of any of both the natural and unnatural amino acids will result in the formation of the desired compounds based on such substitution. Such variations are contemplated to be within the scope of the invention.

Abbreviations which are used in the descriptions of the schemes, preparations and the examples that follow are:

15

THF: Tetrahydrofuran

DMF: *N,N*-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

20

HOObt: 3-Hydroxy-1,2,3-benzotriazin-4(3*H*)-one

EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

NMM: *N*-Methylmorpholine

ADDP: 1,1'-(Azodicarboxyl)dipiperidine

DEAD: Diethylazodicarboxylate

25

MeOH: Methanol

EtOH: Ethanol

Et₂O: Diethyl ether

PyBrOP: Bromo-*tris*-pyrrolidinophosphonium hexafluorophosphate

Bn: Bzl: Benzyl

30

Boc: *tert*-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Ts: p-toluenesulfonyl

Me: Methyl

Bs: p-bromobenzenesulfonyl

5 DCC: dicyclohexylcarbodiimide

DMSO: dimethylsulfoxide

SEM: (trimethylsilyl)ethoxymethyl

TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy free radical

HATU: O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium

10

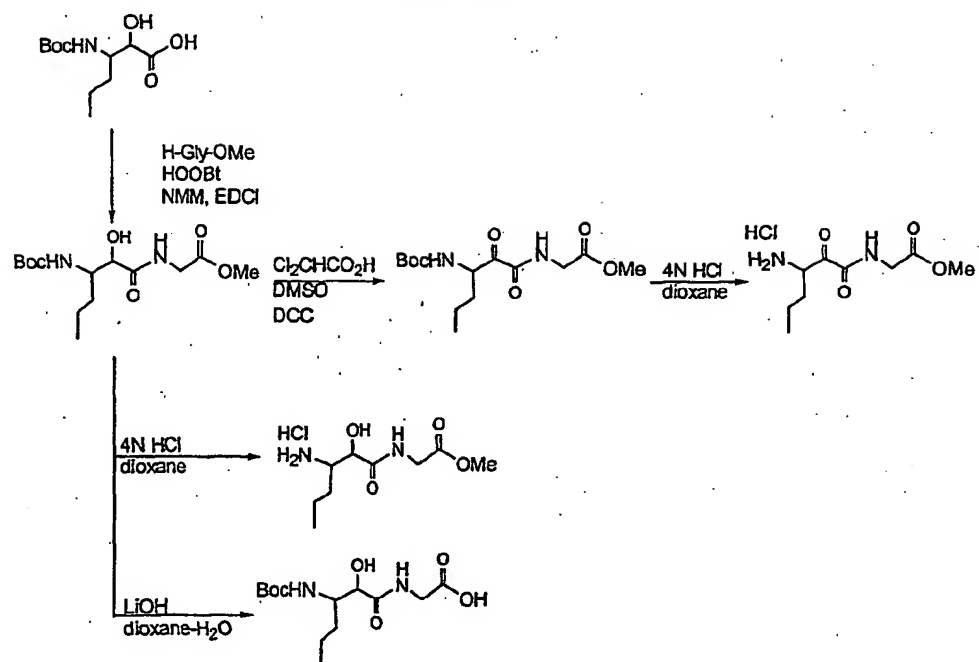
General Preparative Schemes:

The following schemes describe generally methods of synthesis of the intermediates and the inventive diaryl peptides of the present invention.

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SCHEME 1



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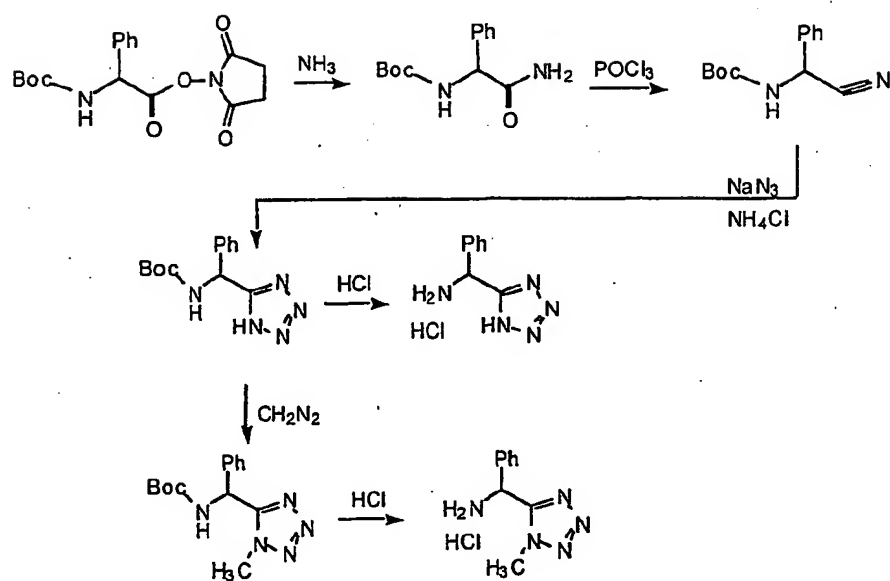
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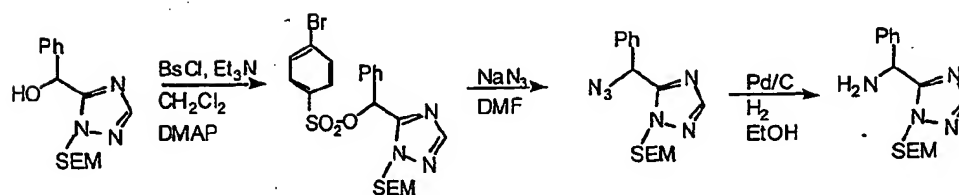
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SCHEME 2



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SCHEME 3

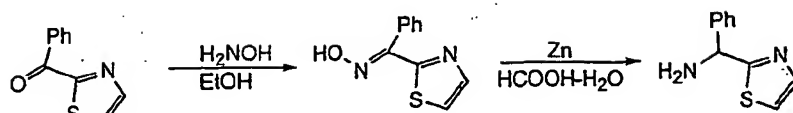


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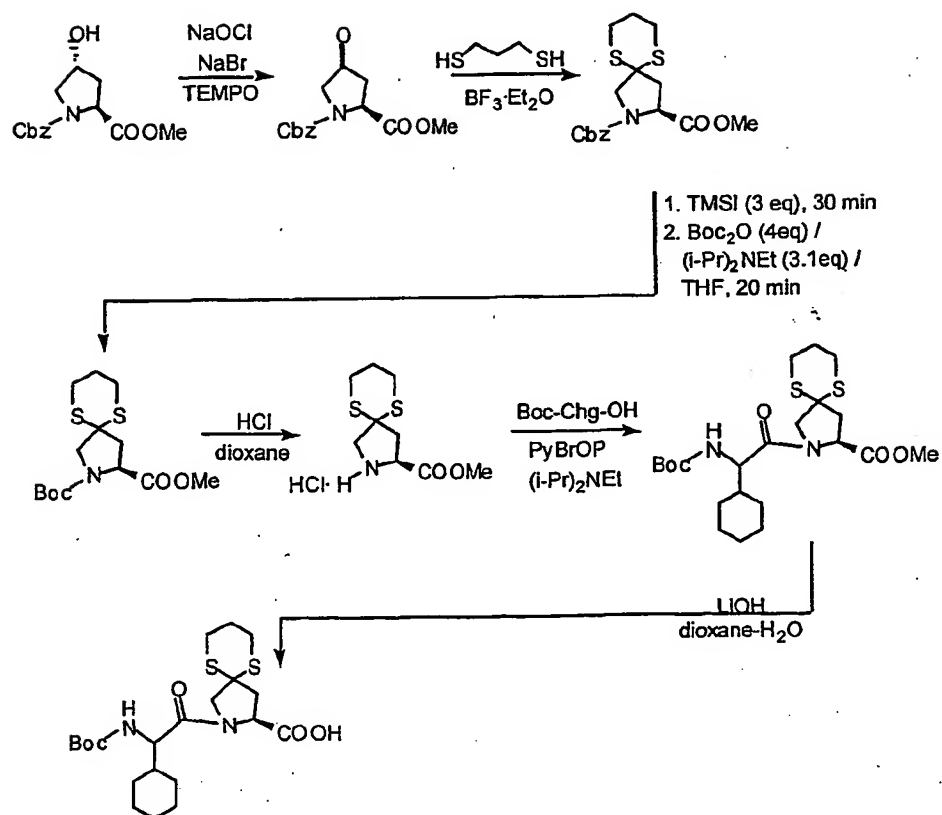
SCHEME 4



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SCHEME 5

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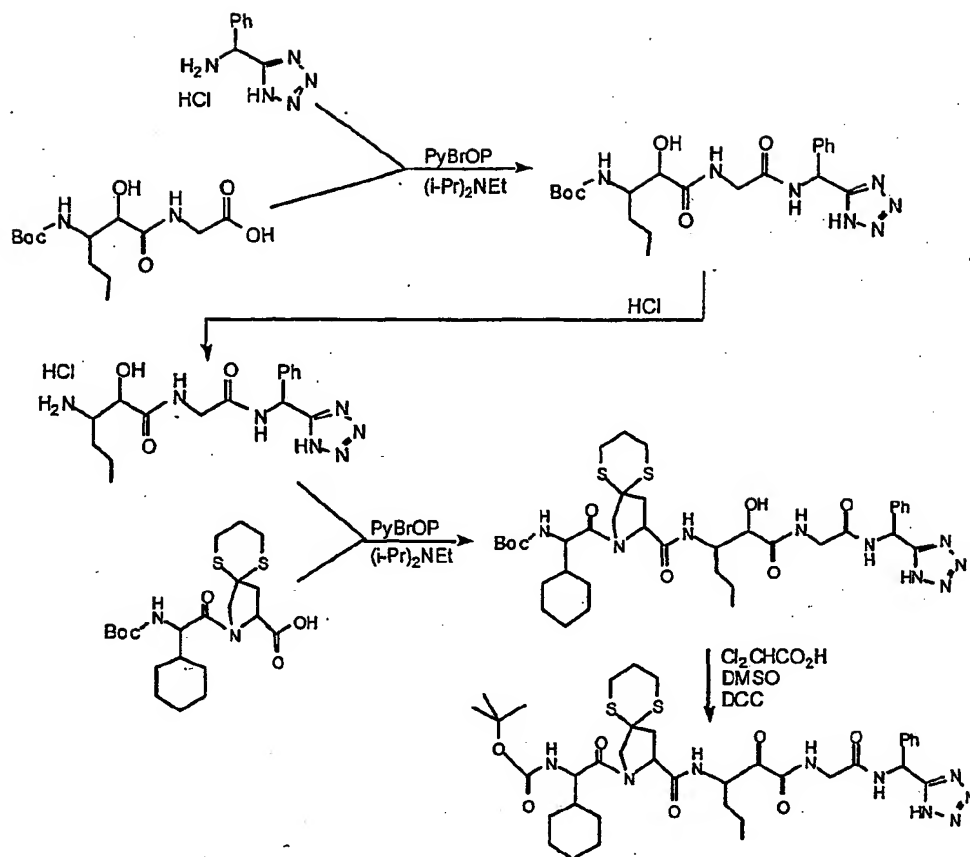


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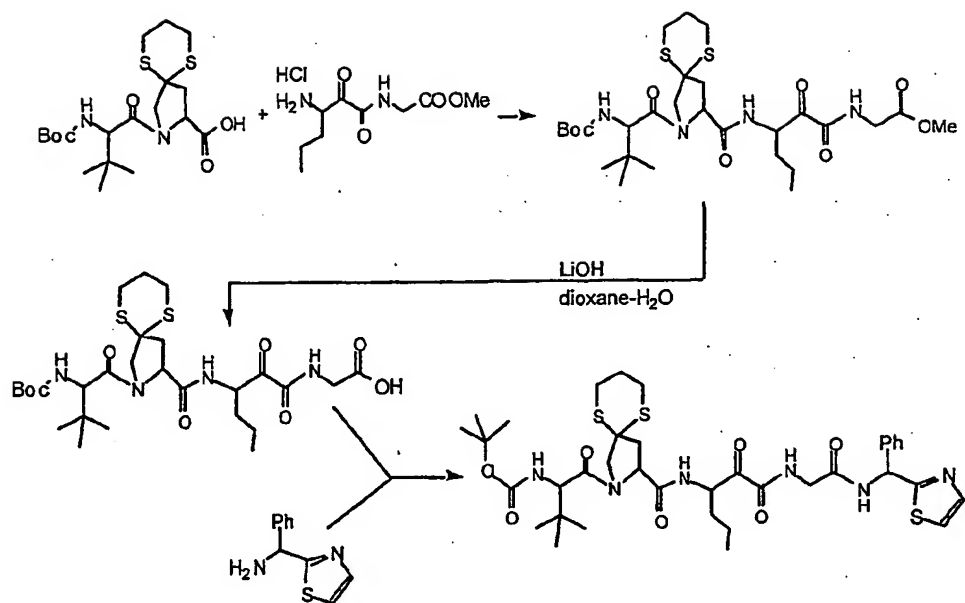
SCHEME 6

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SCHEME 7



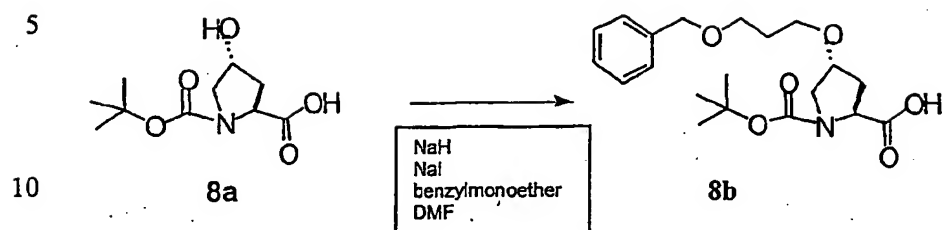
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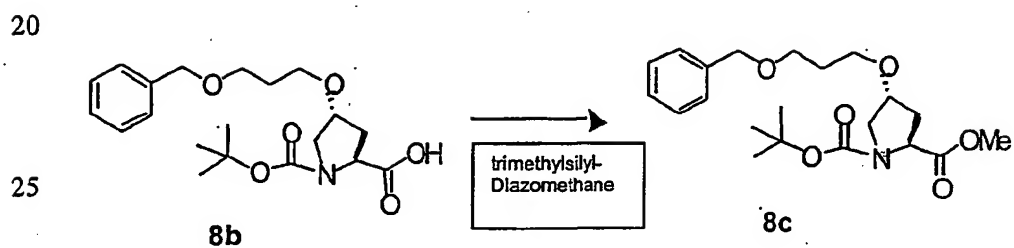
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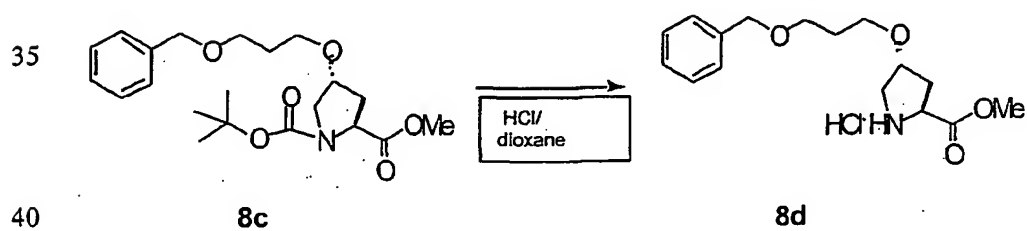
SCHEME 8

Step A

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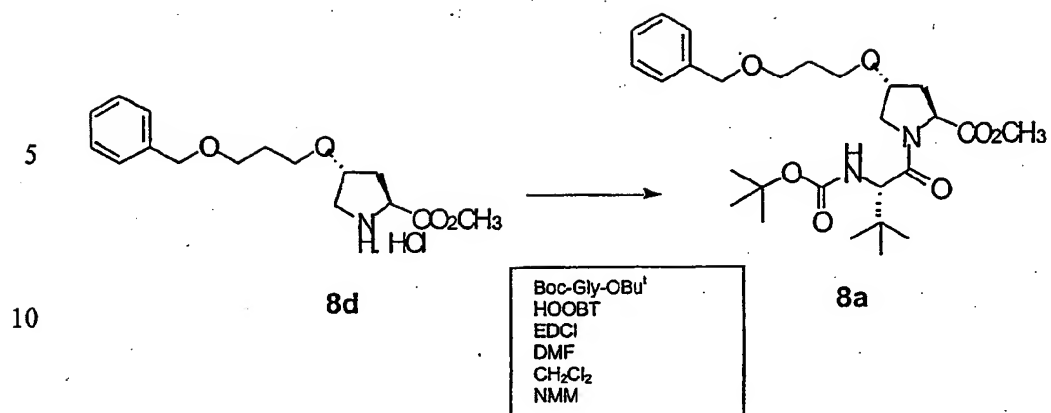
Step B

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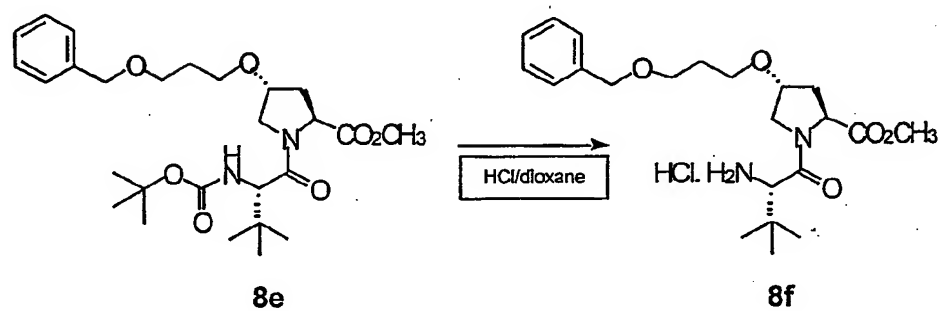
Step CStep D

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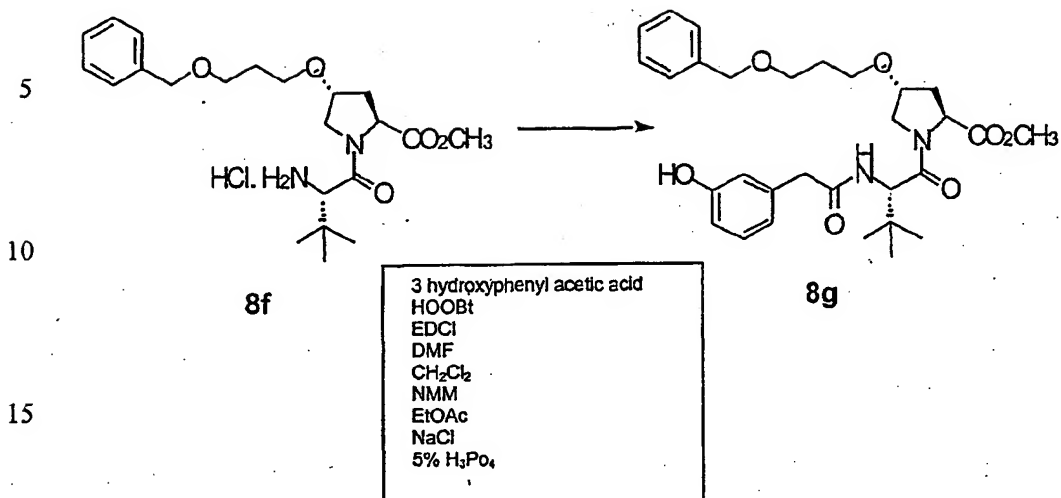
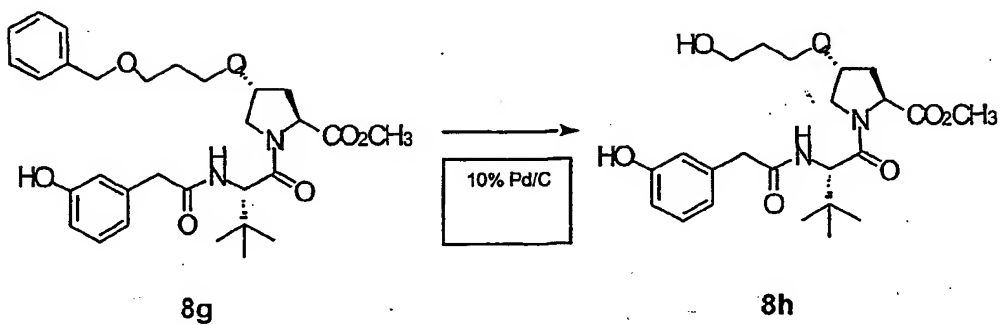
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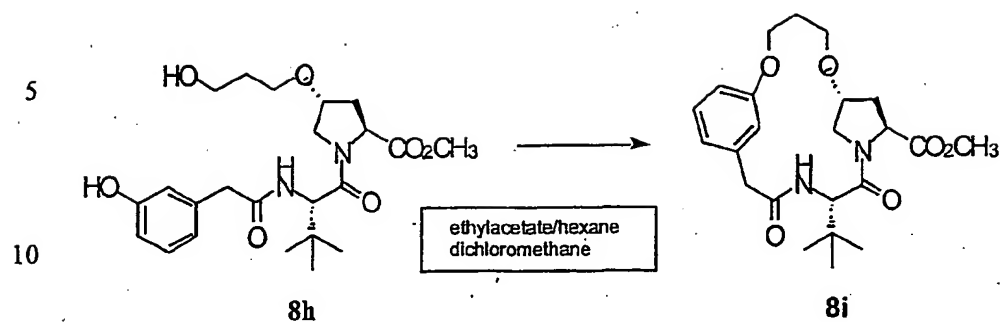
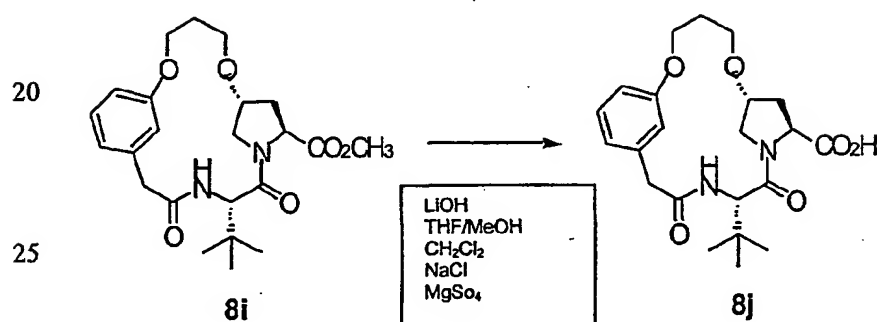
Step E



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Step F20 Step G

60

Step HStep I

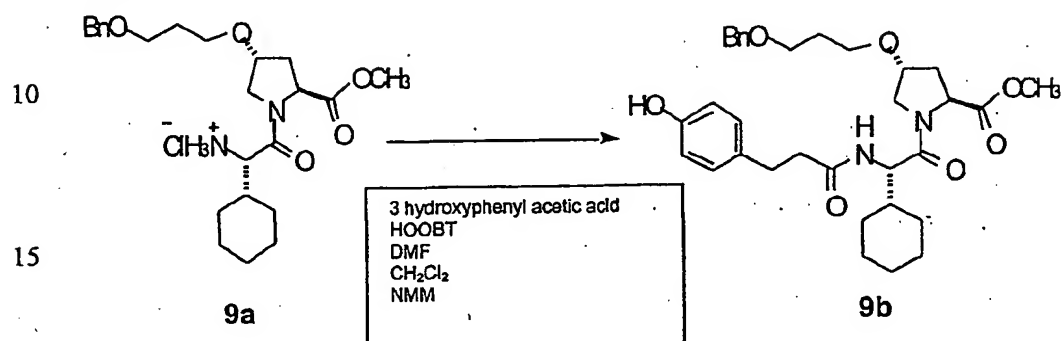
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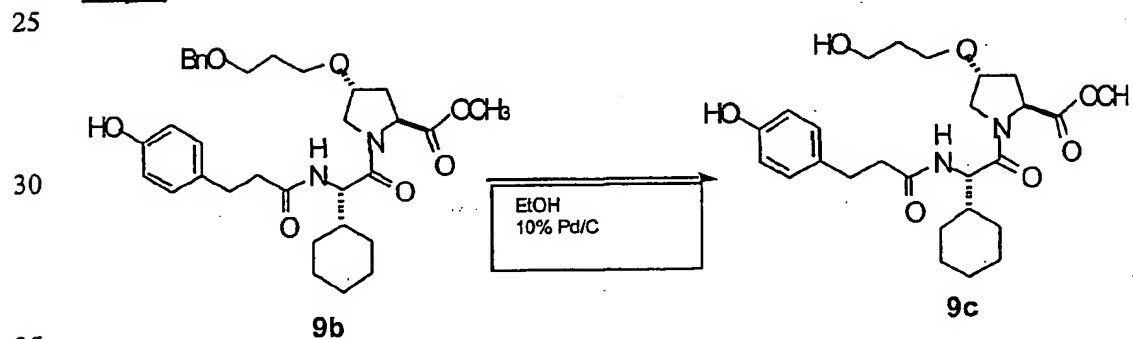
SCHEME 9

Compound 9a was prepared analogous to Scheme 8 Steps A to F.

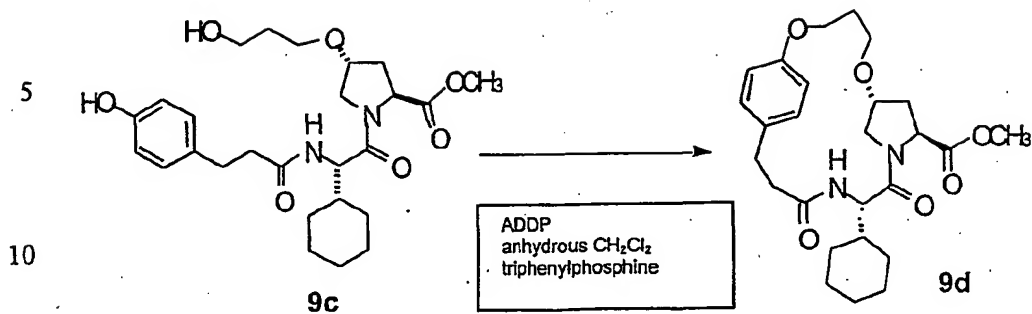
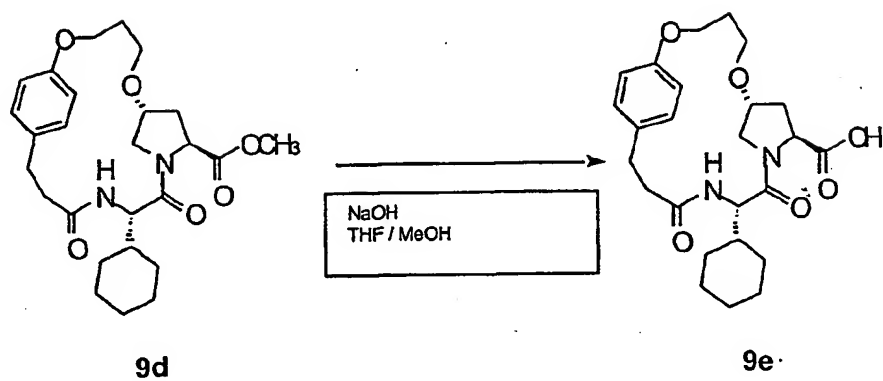
Step A



Step B

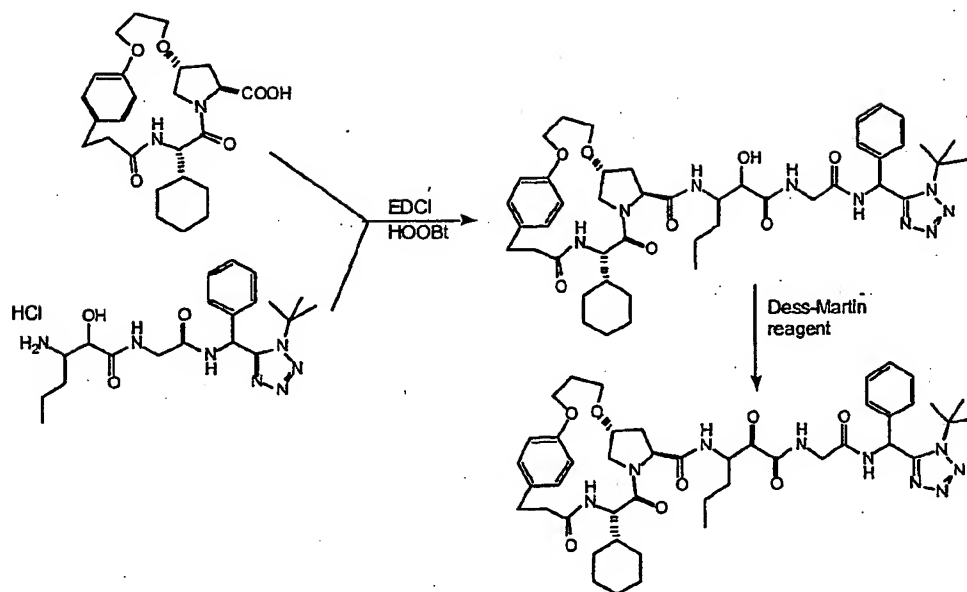


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Step CStep D

SCHEME 10

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Preparation of Intermediates:

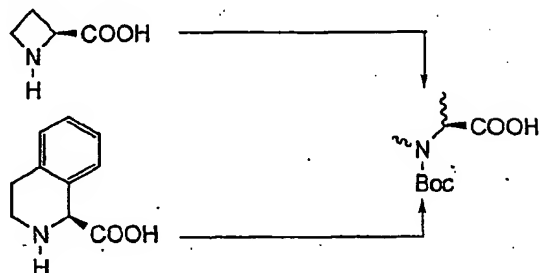
The procedures to modify an amino acid with N-Boc, N-Cbz, COOBzl, COOBu^t, OBzl, OBu^t, COOMe, both putting them on or taking them off in the presence of each other in various combinations, are generally well known to those skilled in the art. Any modifications from the known procedures are noted herein.

15

Commercially available intermediates:

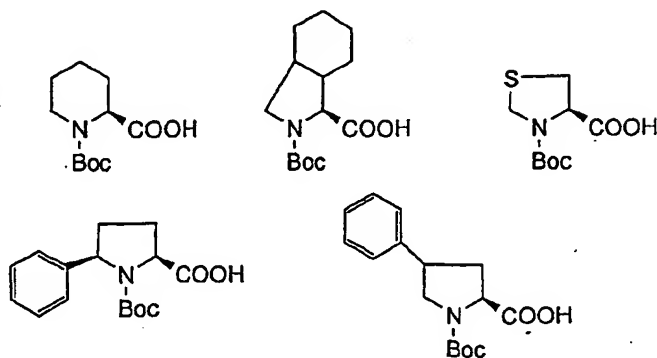
- The following amino acids, used as amino acid units in the preparation of the various inventive compounds, are commercially available, and were converted to their N-Boc derivatives with di-*tert*-butyldicarbonate, using known procedures.

Aldrich Chemical Co.

Tyger Scientific Inc.,
Monmouth Junction, New Jersey

- 10 The following N-Boc-amino acids, used as P2 units, are commercially available.

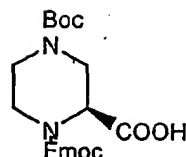
Bachem Biosciences, Inc.

Neosystems,
Princeton, New Jersey

- 15 The following N-Boc-amino acid, used as P2 unit, is commercially available. After coupling the carboxylic acid, the Fmoc is removed by known treatment with piperidine before subsequent coupling.

65

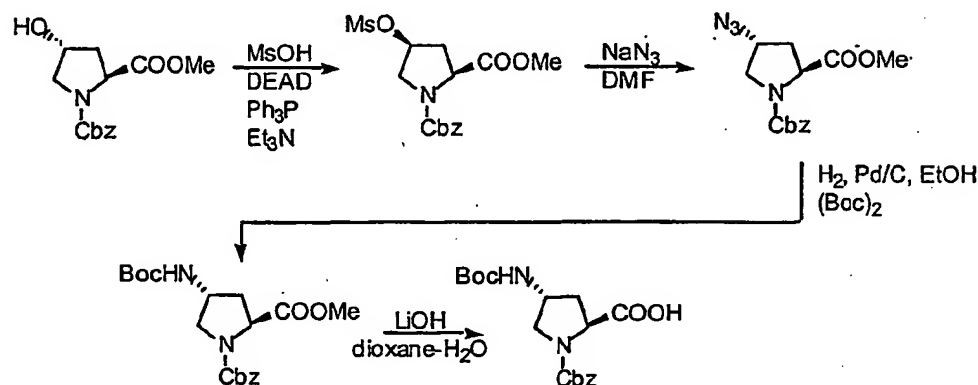
RSP Amino Acid Analogues, Inc.
Worcester, Massachusetts



Example A

Certain intermediates which were not commercially available were
5 synthesized, as needed, by following the procedures given below:

I.



II. Mesylate:

10 A mixture of triphenylphosphine (8.7 g), toluene (200 mL), and
methanesulfonic acid (2.07 mL) was stirred at 15°C while slowly adding
diethylazidodicarboxylate (7.18 g) to maintain the temperature below 35°C.
The mixture was cooled to 20°C, and the N-Boc amino acid (7.4 g,
Bachem Biosciences, Inc.), and Et₃N (1.45 mL) were added, and then the
15 mixture was stirred at 70°C for 5 hr. The mixture was cooled to 5°C, the
organic supernatant decanted, and solvent was removed from it *in vacuo*.
The residue was stirred with Et₂O (200 mL) until a precipitate deposits, the
mixture was filtered, and the ethereal solution was chromatographed on
silica gel (5:95 to 20:80 EtOAc-Et₂O) to obtain the product (9.3 g), which
20 was carried into the next step.

III. Azide

Sodium azide (1.98 g) was added to a solution of the product of the step above (9.3 g) in DMF (100 mL), and the mixture stirred at 70 °C for 8 hr. The mixture was cooled, and poured into 5% aqueous NaHCO₃, and
5 extracted with EtOAc. The organic layer was washed with brine, then dried over anhydrous MgSO₄. The mixture was filtered, and the filtrate evaporated *in vacuo*, to obtain the product (6.2 g), which was carried into the next step.

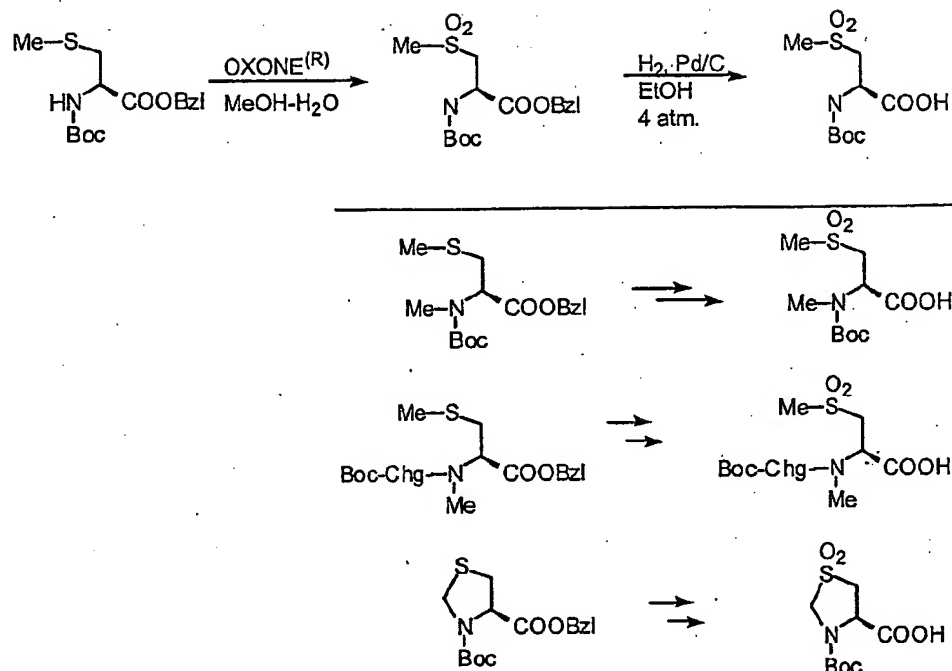
IV. N-Cbz(4-N-Boc)-OMe

10 A solution of the product of the step above (0.6 g) in dioxane (40 mL) was treated with di-*tert*-butyldicarbonate (0.8 g), 10% Pd-C (0.03g), and hydrogen at one atmosphere for 18 hr. The mixture was filtered, the filtrate evaporated *in vacuo*, and the residue chromatographed on silica gel (1:1 to 2:1 Et₂O-hexane) to obtain the product.

15 V. N-Cbz(4-N-Boc)-OH was prepared using known ester hydrolysis using LiOH.

VI. Sulfones by Oxidation:

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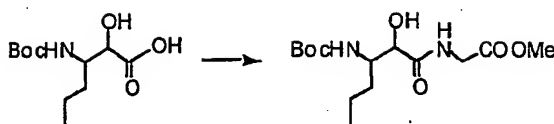


These were prepared by following the procedure of U. Larsson, *et al.*, *Acta Chem. Scan.*, (1994), 48(6), 517-525. A solution of oxone^(R) (20.2 g, from Aldrich Chemical Co.) in water (110 mL) was added slowly to a

5 0°C solution of the sulfide (7.2 g, from Bachem Biosciences, Inc.) in MeOH (100 mL). The cold bath was removed and the mixture stirred for 4 hr. The mixture was concentrated to 1/2 volume on a rotary evaporator, cold water (100 mL) added, extracted with EtOAc, the extract washed with brine, and then it was dried over anhydrous MgSO₄. The mixture was

10 filtered, and the filtrate evaporated *in vacuo*, to obtain the product as a white solid (7.7 g). A portion was crystallized from (*i*-Pr)₂O to obtain an analytical sample, $[\alpha]_D +8.6$ (c 0.8, CHCl₃). Using the same procedure, the other sulfides shown were oxidized to sulfoxes to lead to the subject targets.

Example 1
Step A.



5

1A

To a stirred solution of compound (4.01) (12 g) prepared according to S. L. Harbeson *et al.*, *J. Med. Chem.* 37 (18), 2918-2929 (1994), in
 10 CH₂Cl₂ (150 mL) at -20°C was added HOOBt (7.5 g), *N*-methyl morpholine (6.0 mL) and EDCI (10 g). The reaction mixture was stirred for 10 minutes, followed by the addition of HCl·H₂N-Gly-OMe (6.8 g). The resulting solution was stirred at -20°C for 2 hrs, then kept at 8°C overnight. The solution was concentrated to dryness, then diluted with EtOAc (150
 15 mL). The EtOAc solution was then washed twice with saturated NaHCO₃, H₂O, 5% H₃PO₄, and brine, dried over Na₂SO₄, filtered and concentrated to dryness to give the product, C₁₄H₂₆N₂O₆ (318.37) LRMS *m/z* MH⁺= 319.3.

20 Example 1
Step B



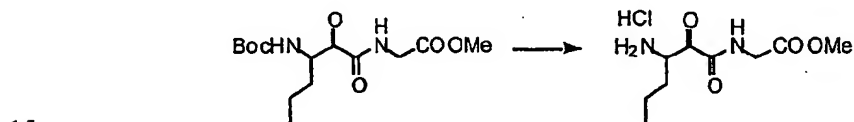
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1B

A mixture of the product from Step A above (5.7 g), dichloromethane (200 mL), methyl sulfoxide (12 mL), and 2,2-dichloroacetic acid (3.2 mL) was stirred at 5°C. To this was added a solution of 1 M dicyclohexylcarbodiimide in CH₂Cl₂ (23 mL), and the

resulting mixture was stirred cold for 5 min., at room temperature for 3 h. A solution of oxalic acid (0.6 g) in methanol (6 mL) was added to destroy excess oxidant, stirred for 15 min., and then filtered to remove the precipitated urea. The filtrate was concentrated *in vacuo*, the remainder
5 diluted with excess ethyl acetate, and washed with cold 0.1 N NaOH, then cold 0.2 N H₃PO₄, then brine. The organic solution was dried over anhydrous MgSO₄, filtered, and evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with a gradient of EtOAc-CH₂Cl₂ (5:95 to 1:1) to obtain the title compound as an oil which solidifies to a wax
10 slowly on standing (5 g, 88% yield) C₁₄H₂₄N₂O₆ (316.35),

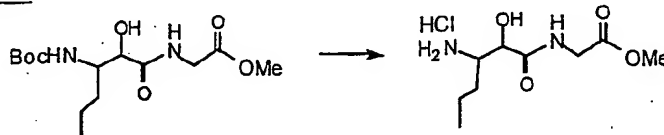
Example 1
Step C



1C

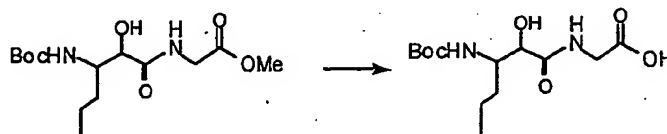
Treat the product of the previous step with a 4N solution of HCl in dioxane (Aldrich Chemical Co.) for 0.5 hr. concentrate the filtrate *in vacuo* in a 30°C water bath, and triturate the residue with Et₂O. Filter the mixture
20 to leave the product compound as a white powder, C₉H₁₆N₂O₄·HCl (252.70), which was used subsequently without further purification.

25 Example 1
Step D



Use the procedure of step C. above to treat the product of step A. above to obtain the product as a white powder, $C_9H_{18}N_2O_4 \cdot HCl$ (254.71).

5 Example 1
 Step E



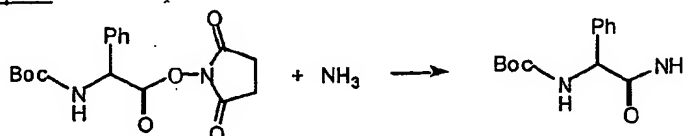
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1E

Treat a solution of the product from Step A. above (8.3 g) in dioxane (150 mL) at 20°C with 1N aqueous LiOH (26 mL) and stir for 2 h. Pour the mixture into a solution of 10% aqueous KH_2PO_4 (500 mL), H_3PO_4 (2 mL), and saturated brine (300 mL); and then extract with EtOAc. Wash the extract with brine, dry it anhydrous $MgSO_4$, filter the mixture, and evaporate the filtrate *in vacuo* to leave the product as a white powder, $C_{13}H_{24}N_2O_6$ (304.34), LRMS (FAB) $M+1 = 305.3$.

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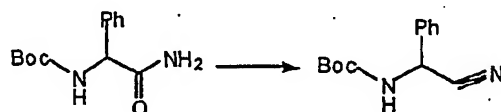
Example 2
 Step A.



25 Treat a solution of N-Boc-phenylglycine N-hydroxysuccinimide ester (1.66 g; Bachem Biosciences, Inc.) in dichloromethane (CH_2Cl_2 , 20 mL) with a solution of 0.5 M NH_3 /dioxane (Aldrich Chemical Co.) (18.5 mL) at 5°C, then allow to warm and stir at room temperature for 4 hr. Suction-filter the mixture, add the filtrate to aq. 5% KH_2PO_4 (150 mL), then extract

with ethyl acetate (EtOAc, 200 mL). Wash the extract twice with aq. 5% KH_2PO_4 , then with saturated brine. Dry the extract over anhydrous MgSO_4 , filter the mixture, and concentrate the filtrate *in vacuo* to leave the crude title compound (1.15 g), which was used immediately in the next step.

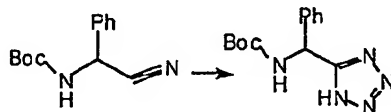
Example 2
Step B.



10

Treat a solution of the product of the previous step (1.15 g) in pyridine (10 mL) at 5°C with POCl_3 (0.6 mL), then allow to warm and stir at room temperature for 3 hr. Pour the mixture onto ice (100 g), then extract with ethyl acetate (2 x 100 mL). Wash the extract with ice-cold 0.1 N H_3PO_4 , then with saturated brine. Dry the extract over anhydrous MgSO_4 , filter the mixture, and concentrate the filtrate *in vacuo*. Crystallize the residue from hexane to obtain the title compound (0.66 g, 60% yield overall).

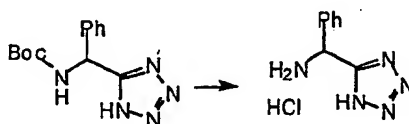
20 Example 3
Step A.



Treat a solution of the product of the previous step (0.18 g) in DMF (2 mL) with NaN_3 (0.055 g) and NH_4Cl (0.045 g), then stir at 90°C for 6 hr. Cool the reaction mixture, quench it with 10% aqueous KH_2PO_4 , then extract with ethyl acetate (2 x 35 mL). Wash the extract with 10% aqueous KH_2PO_4 , then with saturated brine. Dry the extract over

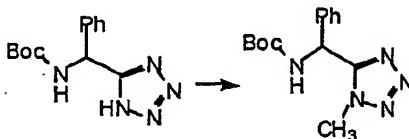
anhydrous MgSO_4 , filter the mixture, and concentrate the filtrate *in vacuo* to leave the crude title compound, which was used in the next step without further purification; $\text{C}_{13}\text{H}_{17}\text{N}_5\text{O}_2$ (275.31); LRMS (FAB) $M+1 = 276.2$.

5 Example 3
 Step B



10 Use the procedure of Example 1 Step C. above to treat the product of the previous step to obtain the product as a white powder, which is used subsequently without further purification.

15 Example 4
 Step A.



4A

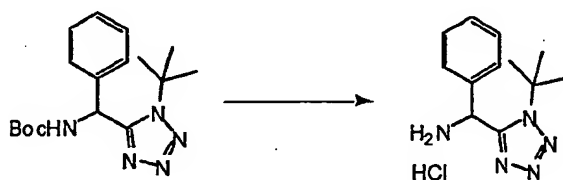
20 Treat a solution of the product of Example 2a. (0.055 g) and THF (1.5 mL) at 5°C with excess of a solution of diazomethane in Et_2O . Allow the solution to warm to room temperature over 2 hr., quench with hexane, and concentrate the filtrate *in vacuo* to leave the crude title compound (0.056 g), which was used without further purification; $\text{C}_{14}\text{H}_{19}\text{N}_5\text{O}_2$ (Mol. Wt.: 289.33), LRMS (FAB) $M+1 = 290.0$.

25

Example 4Step B.

- 5 Use the procedure if Example 1 Step C. above to treat the product of the preceding step (0.055 g) to obtain the product as a white powder (0.027 g), as a 3:1 mixture of regioisomers, $C_9H_{11}N_5 \cdot HCl$ (225.68) 1H NMR (DMSO- d_6) δ 9.3 (br s, 3 H), 7.45 (m, 5 H), 6.22 (s, 0.3 H) and 6.03 (s, 0.7 H), 4.39 (s, 2.1 H) and 3.94 (s, 0.9 H).

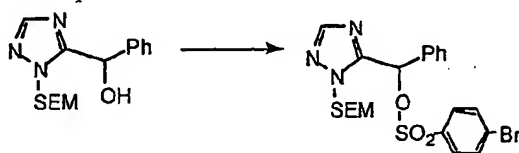
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Example 5

- 15 Following the procedure of Example 1, Step C above, the product of the previous Step was converted to the corresponding product, which is used subsequently without further purification.

Example 6Step A

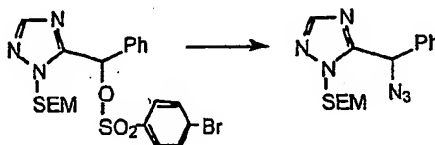
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- 25 4-bromobenzenesulfonyl chloride (7.1 g) was added to a solution of the ethyl alcohol (N. Fugina, et al., Heterocycles, **1992**, 34(2), 303-314) at 0°C, followed by Et₃N (3.9 mL) and DMAP (3.4 g), and stir the mixture for 18 hr. at ambient temperature. Wash the reaction mixture with 10%

aqueous KH_2PO_4 , then brine, and dry the solution over anhydrous MgSO_4 . Filter the mixture, evaporate solvent *in vacuo*, and chromatograph the residue on silica gel (15:85 EtOAc- CH_2Cl_2) to obtain the product (3.6 g) $\text{C}_{21}\text{H}_{26}\text{BrN}_3\text{O}_4\text{SSi}$ (524.51) LRMS (FAB) $\text{M}+\text{H}=524.2$.

Example 6
Step B



Stir a mixture of the product from the step above (3.6 g), sodium azide (0.56 g), and DMF (50 mL) at 100°C for 4 hr. Pour the cooled reaction mixture into cold water, extract with EtOAc, wash the extract with brine, and dry it over anhydrous MgSO_4 . Filter the mixture, evaporate solvent *in vacuo*, and chromatograph the residue on silica gel (3:97 EtOAc- CH_2Cl_2) to obtain the product (2.8 g) $\text{C}_{15}\text{H}_{22}\text{N}_6\text{OSi}$ (330.47) LRMS (FAB) $\text{M}+\text{H}=331.2$.

Example 6
Step C



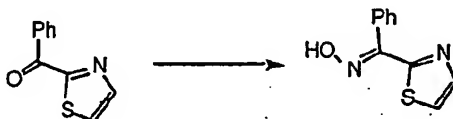
Treat a solution of the product from the step above (1.3 g) in EtOH (50 mL) with 10% Pd-C (0.15 g) and hydrogen at 1 atm. for 18 hr. Filter

75

the mixture and evaporate solvent *in vacuo* to leave the product (1.2 g)
 $C_{15}H_{24}N_4OSi$ (304.47) LRMS (FAB) $M+H=305.3$.

Example 7

Step A



A stirred solution of 2-benzoylthiazole (1.9 g, G. Jones, et al.,
Tetrahedron, 1991, 47 (16), 2851-2860.) in EtOH:H₂O (50:5 mL) was
10 treated with hydroxylamine hydrochloride (1.4 g), and heated at reflux for
24 hr. The cooled mixture was poured into EtOAc and washed
successively with 10% aqueous KH₂PO₄, then brine. The extract was
dried over anhydrous MgSO₄, the mixture was filtered, and the solvent
was evaporated *in vacuo* to leave the product as a mixture of geometric
15 isomers, $C_{10}H_8N_2OS$ (204.25) LRMS (FAB) $M+1=205.2$.

Example 7

Step B



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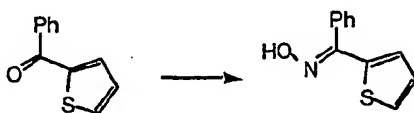
The product of the preceding step was mixed with MeOH (30 mL),
formic acid (15 mL), and water (15 mL), and cooled to 0°C. Zinc dust was
added in small portions to the stirred mixture over 0.5 hr., and the mixture
25 was stirred an additional 18 hr. at 0°C. The mixture was then suction-
filtered through a celite pad, and the filtrate was evaporated *in vacuo*. The
gum residue was taken up with EtOAc (0.5 L) and 1 N NaOH (0.1 L), the
mixture again suction-filtered, and the aqueous layer of the filtrate

76

discarded. The organic extract was washed with brine and dried over anhydrous MgSO_4 . The mixture was filtered, the solvent was evaporated *in vacuo*, and the residue was chromatographed (silica gel, 1:1 EtOAc: CH_2Cl_2) to give the product, $\text{C}_{10}\text{H}_{10}\text{N}_2\text{S}$ (190.27) LRMS (FAB)

5 M+1=191.1.

Example 8
Step A

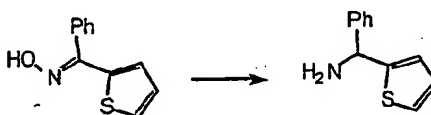


10

Following the procedure of Example 6 step A. above, 2-benzoylthiophene (C. Malanga, et al., *Tetrahedron Lett.*, **1995**, 36 (50), 9185-9188) was converted to the corresponding product, $\text{C}_{11}\text{H}_9\text{NOS}$

15 (203.26), LRMS (FAB) M+1=204.2.

Example 8
Step B



20

Following the procedure of Example 6 step B. above, the product of the preceding step was converted to the corresponding product, $\text{C}_{11}\text{H}_{11}\text{NS}$ (189.28), LRMS (FAB) M+1=190.2.

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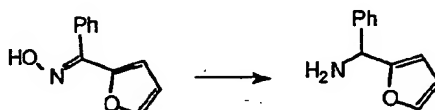
Example 9
Step A



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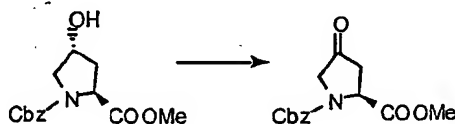
Following the procedure of Example 6 step A. above, 2-benzoylfuran (M. J. Aurell, et al., *J.Org.Chem.*, **1995**, 60 (1), 8-9) was converted to the corresponding product, C₁₁H₉NO₂ (187.19), 188.1.

10 Example 9
Step B



15 Following the procedure of Example 6 step B. above, the product of the preceding step was converted to the corresponding product, C₁₁H₁₁NO (173.21), LRMS (FAB) M+1=174.2.

20 Example 10
Step A



25 Combine N-Cbz-hydroxyproline methyl ester (available from Bachem Biosciences, Incorporated, King of Prussia, Pennsylvania), compound (2.1) (3.0 g), toluene (30 mL), and ethyl acetate (30 mL). The mixture was stirred vigorously, and then a solution of NaBr/water (1.28 g /5 mL) was added. To this was added 2,2,6,6-tetramethyl-1-piperidinyloxy

78

free radical (TEMPO, 17 mg, from Aldrich Chemicals, Milwaukee, Wisconsin). The stirred mixture was cooled to 5°C and then was added a prepared solution of oxidant [commercially available bleach, Clorox® (18 mL), NaHCO₃ (2.75 g) and water to make up 40 mL] dropwise over 0.5 hr.

5 To this was added 2-propanol (0.2 mL). The organic layer was separated, and the aqueous layer extracted with ethyl acetate. The organic extracts were combined, washed with 2% sodium thiosulfate, then saturated brine. The organic solution was dried over anhydrous MgSO₄, filtered, and evaporated the filtrate under vacuum to leave a pale yellow gum suitable

10 for subsequent reactions (2.9 g, 97% yield), C₁₄H₁₅NO₅ (277.28), mass spec. (FAB) M+1 = 278.1.

Example 10
Step B

15



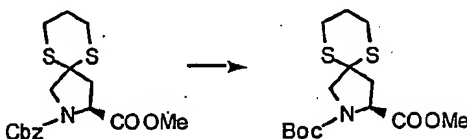
Compound (2.2) from Step A above (7.8 g) was dissolved in dichloromethane (100 mL), and cooled to 15°C. To this mixture was first

20 added 1,3-propanedithiol (3.1 mL), followed by freshly distilled boron trifluoride etherate (3.7 mL). The mixture was stirred at room temperature for 18 h. While stirring vigorously, a solution of K₂CO₃/water (2 g / 30 mL) was carefully added, followed by saturated NaHCO₃ (10 mL). The organic layer was separated from the aqueous layer (pH ~7.4), washed

25 with water (10 mL), then brine. The organic solution was dried over anhydrous MgSO₄, filtered, and evaporated under vacuum. The residue was chromatographed on silica gel, eluting with toluene, then a with a

gradient of hexane-Et₂O (2:3 to 0:1) to afford a brown oil (7.0 g, 68% yield), C₁₇H₂₁NO₄S₂ (367.48), mass spec. (FAB) M+1 = 368.1.

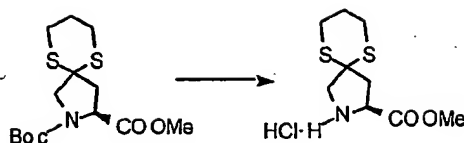
Example 10
Step C



A solution of compound (2.3) from Step B above (45 g) in
10 acetonitrile (800 mL) at 20°C was treated with freshly distilled
iodotrimethylsilane (53 mL) at once. The reaction was stirred for 30 min.,
then poured into a freshly prepared solution of di-*t*-butyldicarbonate (107
g), ethyl ether (150 mL), and diisopropylethylamine (66.5 mL). The
mixture stirred for 30 min. more then was washed with hexane (2 x 500
15 mL). Ethyl acetate (1000 mL) was added to the lower acetonitrile layer,
and then the layer was washed with 10% aqueous KH₂PO₄ (2 x 700 mL),
and brine. The filtrate was evaporated under vacuum in a 25°C water
bath, taken up in fresh ethyl acetate (1000 mL), and washed successively
with 0.1 N HCl, 0.1 N NaOH, 10% aqueous KH₂PO₄, and brine. The
20 organic solution was dried over anhydrous MgSO₄, filtered, and
evaporated under vacuum. The residue (66 g) was chromatographed on
silica gel (2 kg), eluting with hexane (2 L), then Et₂O/hexane (55:45, 2 L),
then Et₂O (2 L) to afford an orange gum which slowly crystallized on
standing (28 g, 69% yield), C₁₄H₂₃NO₄S₂ (333.46), mass spec. (FAB)
25 M+1 = 334.1.

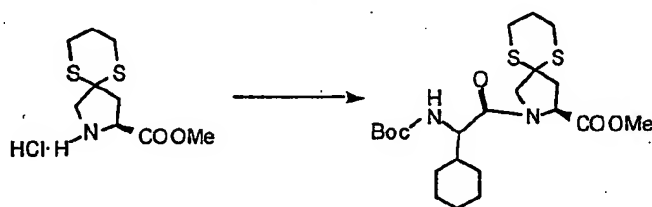
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Example 10
Step D



5

To a solution of compound (2.4) from Step C above (1 g) in dioxane (5 mL), was added 4 N HCl-dioxane solution (50 mL). The mixture was stirred vigorously for 1 hr. The mixture was evaporated under vacuum in a 25°C water bath. The residue was triturated with Et₂O, and filtered to
10 leave the title compound (0.76 g, 93% yield), C₉H₁₅NO₂S₂·HCl (269.81), mass spec. (FAB) M+1 = 234.0.



15 Example 10
Step E

10E

A mixture of compound (2.6) from Step E above (1.12 g), N-Boc-cyclohexylglycine (Boc-Chg-OH, 1.0 g, from Sigma Chemicals, St. Louis, Missouri), dimethylformamide (20 mL), and PyBrOP coupling reagent (2.1 g) was cooled to 5°C. To this was added diisopropylethylamine (DIEA or DIPEA, 2.8 mL). The mixture was stirred cold for 1 min., then stirred at room temperature for 6 hr. The reaction mixture was poured into cold 5%
25 aqueous H₃PO₄ (150 mL) and extracted with ethyl acetate (2 x 150 mL). The combined organic layer was washed with cold 5% aqueous K₂CO₃,

then 5% aqueous KH_2PO_4 , then brine. The organic solution was dried over anhydrous MgSO_4 , filtered, and evaporated under vacuum. The residue was chromatographed on silica gel, eluting with $\text{EtOAc-CH}_2\text{Cl}_2$ to afford a white solid (0.8 g, 50% yield), $\text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_5\text{S}_2$ (472.66), mass spec. (FAB) $\text{M}+1 = 473.2$.

Example 10
Step F



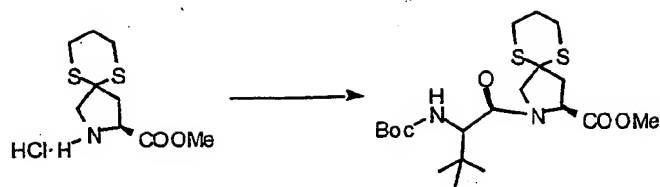
10

A solution of compound (?) from Step ? above (0.8 g) in dioxane (10 mL) at 20°C was treated with 1N aqueous LiOH (3.4 mL) and stirred for 4 h. The mixture was concentrated under vacuum in a 30°C water bath to half volume. The remainder was diluted with water (25 mL), extracted with Et_2O (2 x 20 mL). The aqueous layer was acidified to pH ~ 4 with 6 N HCl , extracted with ethyl acetate, and washed with brine. The organic solution was dried over anhydrous MgSO_4 , filtered, and evaporated under vacuum to leave the title compound (2.8) (0.7 g), $\text{C}_{21}\text{H}_{34}\text{N}_2\text{O}_5\text{S}_2$ (458.64), mass spec. (FAB) $\text{M}+1 = 459.2$.

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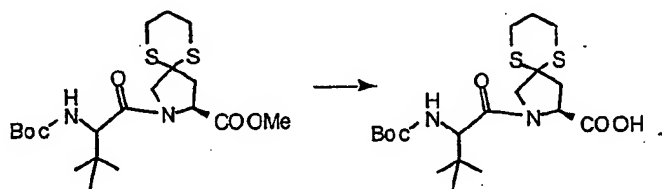
82

Example 12
Step A



- 5 Following the procedure of Example 10 step E. above, N-Boc-Tle-OH (Bachem Biosciences, Inc.) and the product of Example 9 step D. were reacted to give the corresponding product, $C_{20}H_{34}N_2O_5S_2$ (446.63), LRMS (FAB) $M+1 = 447.3$.

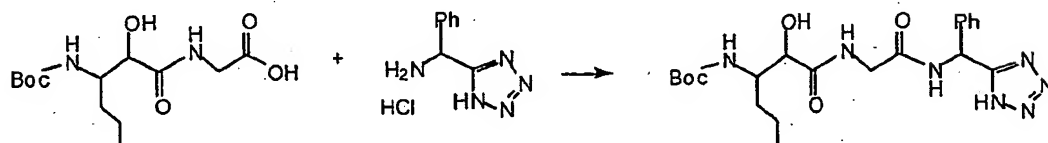
10 Example 12
Step B



- 15 Following the procedure of Example 10 step E. above, the product of the preceding step was converted to the corresponding product, $C_{19}H_{32}N_2O_5S_2$ (432.60), LRMS (FAB) $M+1 = 433.3$.

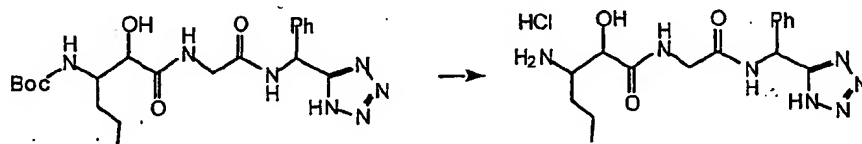
Example 12
Step A

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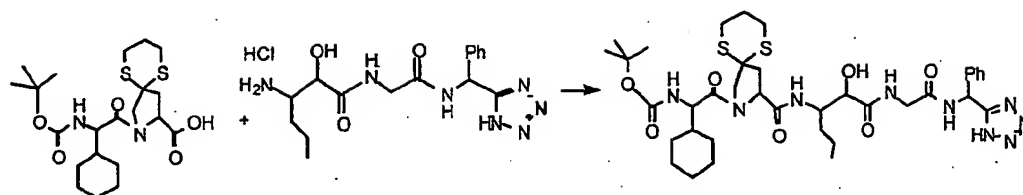
Cool a stirred mixture of the product of the previous step (0.11 g), the product of Example-1 Step E. above [Boc-Nva(OH)-Gly-OH] (0.205 g), dimethylformamide (7 mL), and PyBrOP coupling reagent (0.385 g) to 5°C, then add diisopropylethylamine (DIPEA, 0.252 mL). Stir the mixture cold for 1 min., then stir at room temperature for 6 hr. Pour the reaction mixture into cold 1% aqueous H₃PO₄ (150 mL) and extract with ethyl acetate. Wash the combined organics with cold 5% aqueous K₂CO₃, then 5% aqueous KH₂PO₄, then brine. Dry the organic solution over anhydrous MgSO₄, filter, and evaporate the filtrate *in vacuo* to leave the crude title compound (0.15 g), which was used in the next step without further purification.

Example 12
Step B



Treat the product of the previous step with a 4N solution of HCl in dioxane for 0.5 hr. concentrate the filtrate *in vacuo* in a 30°C water bath, and triturate the residue with Et₂O. Filter the mixture to leave the title compound as a white powder 90.13 g0, which was used in the next step without further purification; C₁₆H₂₃N₇O₃ (361.40), LRMS (FAB) M+1 = 362.4.

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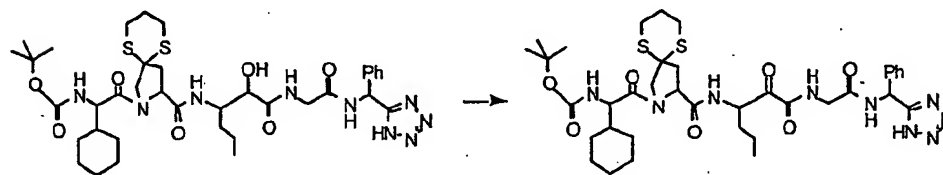
Example 12Step C

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Cool a stirred mixture of the product of Example 5 step B. (0.06 g), the product of Example-8 Step G. (0.85 g), dimethylformamide (8 mL), and PyBROP coupling reagent (0.088 g) to 5°C, then add diisopropylethylamine (DIPEA, 0.89 mL). Stir the mixture cold for 1 min., then stir at room

10 temperature for 48 hr. Pour the reaction mixture into cold 1% aqueous H₃PO₄ and extract with ethyl acetate. Wash the combined organics with 5% aqueous KH₂PO₄, then brine. Dry the organic solution over anhydrous MgSO₄, filter, and evaporate the filtrate *in vacuo* to leave the crude title compound (0.13 g). Chromatograph the residue on silica gel

15 with MeOH-CH₂Cl₂ (1:99 to 10:90 gradient) to obtain the title compound (0.092 g); C₃₇H₅₅N₉O₇S₂ (802.02), LRMS (FAB) M+1 = 802.6.

Example 12Step D

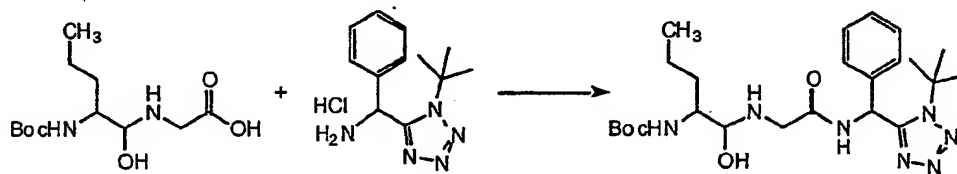
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Cool a solution of oxalyl chloride (25 μ L) and CH₂Cl₂ to -70°C. Add slowly a solution of methyl sulfoxide (DMSO, 50 μ L) and CH₂Cl₂ (1 mL) below -60°C. Cool to -70°C, and add dropwise a solution of the product of

85

the previous step (0.0.09 g) and CH_2Cl_2 (1 mL) below -60°C . Stir an additional 0.5 hr., add slowly triethylamine (Et_3N , 0.13 mL) below -50°C , then warm to 10°C . Dilute the reaction with excess ethyl acetate, and wash the solution with cold 0.1 N HCl, then brine. Dry the organic solution over anhydrous MgSO_4 , filter, and evaporate the filtrate under vacuum. Chromatograph the residue on silica gel, eluting with $\text{MeOH}-\text{CH}_2\text{Cl}_2$ (1:99 to 25:75 gradient) to obtain the title compound (0.011 g, 12% yield), $\text{C}_{37}\text{H}_{53}\text{N}_9\text{O}_7\text{S}_2$ (800.01), LRMS (FAB) $M+1 = 800.3$.

10 Example 13
Step A

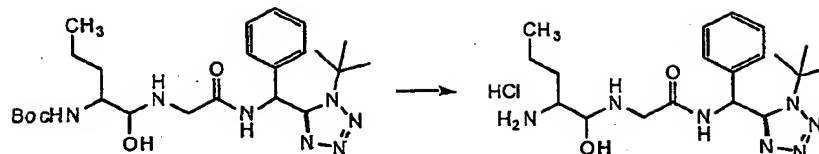


15

A solution of the product of example 1 step E. (100 mg, 0.22 mmols) in dry DMF (2.5 mL) was treated with HOOBt (45 mg, 0.33 mmols) and Hünigs base (141 mg, 1.1 mmols, 5.0 equiv.). The reaction mixture was cooled to -20°C and treated with EDCI (63 mg, 0.33 mmols, 1.5 equiv) and stirred for 20 min. The reaction mixture was treated with amine hydrochloride (118 mg, 0.27 mmols, 1.22 equiv.) and stirred at rt for 12 h. The reaction mixture was concentrated in vacuo and diluted with H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3x50 mL) and EtOAc (3x50 mL). The combined organic layers were extracted with aq. HCl (2M), aq. NaHCO_3 (satd), dried (MgSO_4) filtered concentrated in vacuo to obtain a colorless solid 1k (79 mg) which was used for oxidation; LRMS [electron spray, m/z (rel int)]: $M+1 = 826$ (100).

86

Example 13
Step B

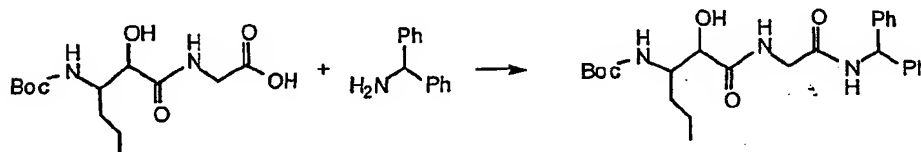


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Following the procedure of Example 12 Step B., the product of the preceding Step was converted to the corresponding product, which was used as it was for subsequent reactions. MS (Electron spray): [835

10 $(2M+1)^+$, 40], 418 $[M+1]^+$, 100]].

Example 14
Step A

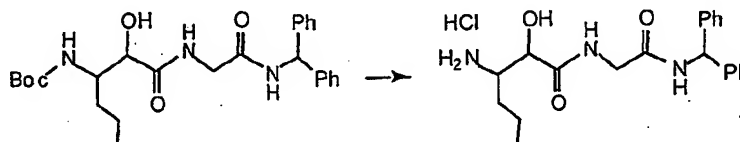


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Following the procedure of Example 12 Step A. above, the product of Example 1 step E. is reacted with benzhydramine to give the corresponding product, C₂₆H₃₅N₃O₅ (469.57), LRMS (FAB) M+1=470.4.

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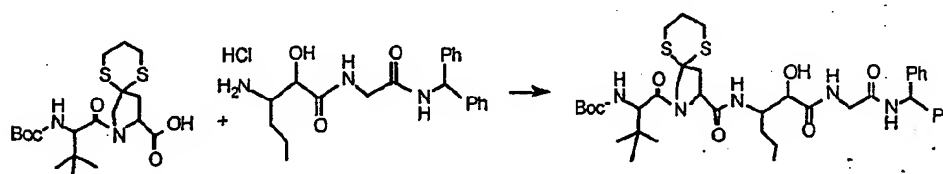
Example 14
Step B



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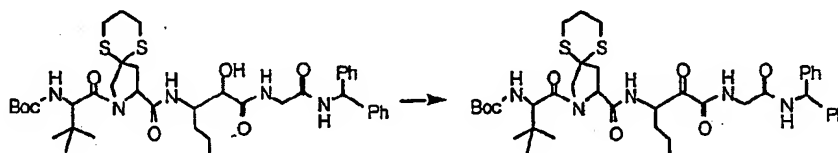
Following the procedure of Example 12 step B., the product of the preceding step was converted to the corresponding product, $C_{21}H_{27}N_3O_3 \cdot HCl$ (405.92), LRMS (FAB) $M+1=370.4$.

5 Example 14
Step C



10 Following the procedure of Example 12 step C., the product of the preceding step was reacted with the product of Example 10 step B. to give the corresponding product, $C_{40}H_{57}N_5O_7S_2$ (784.04), LRMS (FAB) $M+1=784.5$.

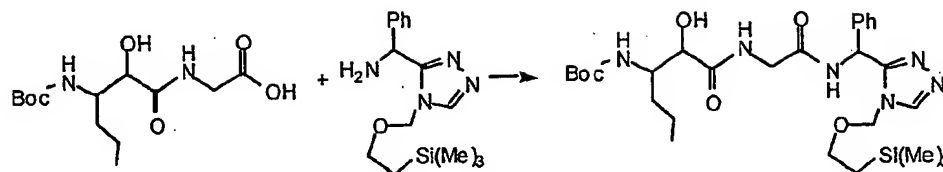
15 Example 14
Step D



20 Following the procedure of Example 12 step D., the product of the preceding step was converted to the corresponding product, $C_{40}H_{55}N_5O_7S_2$ (782.03), LRMS (FAB) $M+1=782.4$.

88

Example 15
Step A

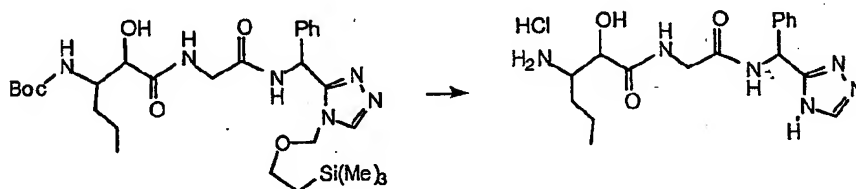


5

Following the procedure of Example 12 Step A. above, the product of Example 1 step E. is reacted with the product of Example 5 step C. to give the corresponding product, $C_{28}H_{46}N_6O_6Si$ (590.79), LRMS (FAB) $M+1=591.4$.

10

Example 15
Step B



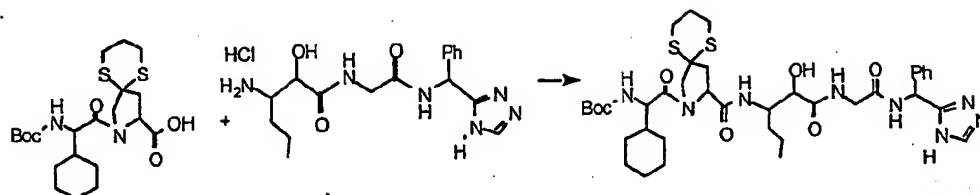
15

Following the procedure of Example 12 Step B., the product of the preceding step was converted to the corresponding product, $C_{17}H_{24}N_6O_3 \cdot HCl$ (396.87), LRMS (FAB) $M+1=361.3$.

20

89

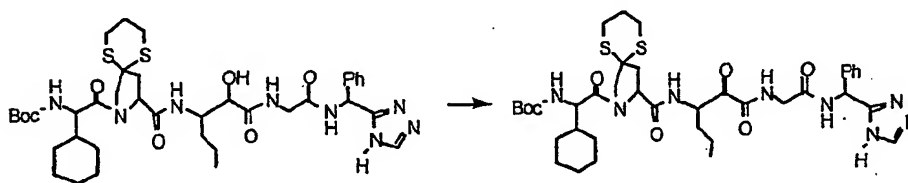
Example 15
Step C



5

Following the procedure of Example 12 Step C., the product of the preceding step was converted to the corresponding product, $C_{38}H_{56}N_8O_7S_2$ (801.03), LRMS (FAB) $M+1=801.5$.

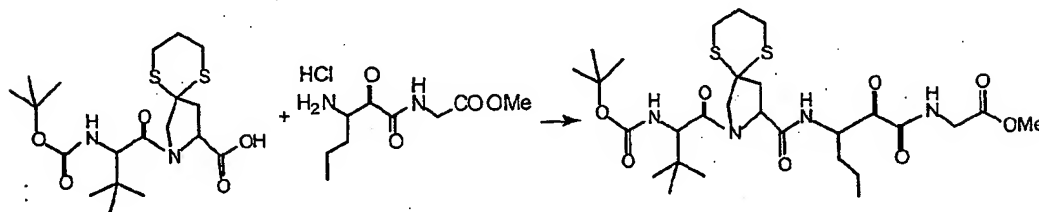
10 Example 15
Step D



15

Following the procedure of Example 12 Step D., the product of the preceding step was converted to the corresponding product, $C_{38}H_{54}N_8O_7S_2$ (809.02), LRMS (FAB) $M+1=799.4$.

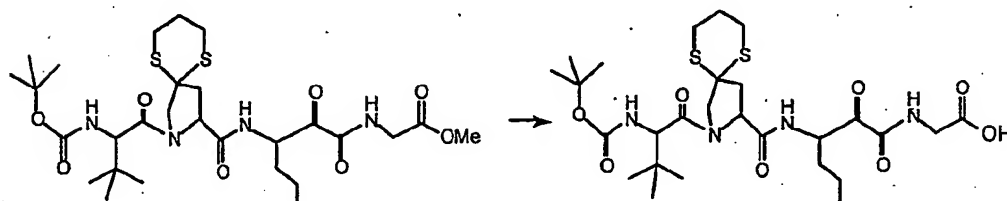
20 Example 16
Step A



Follow the procedure of Example 1A but use the acid of Example Step 10B above and the amine of Example Step 1C to obtain the compound, C₂₈H₄₆N₄O₈S₂ (630.82) LRMS (FAB) M+H = 631.4.

5

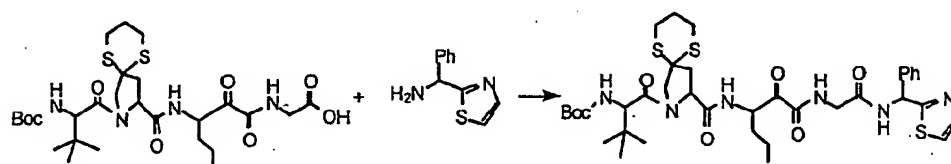
Example 16
Step B



10

Follow the procedure of Example 1 Step E but use the ester of the preceding Step to obtain the compound, C₂₇H₄₄N₄O₈S₂ (616.79) LRMS (FAB) M+H = 617.4.

15 Example 16
Step C



20

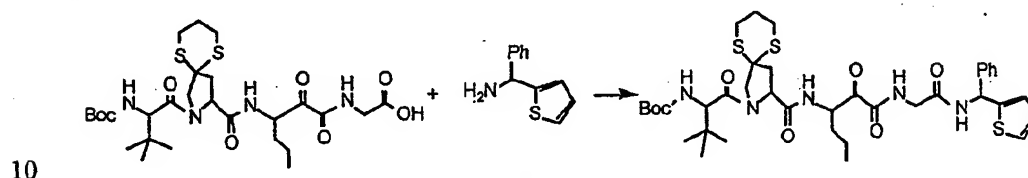
A stirred mixture of the product of the preceding Step (62 mg), the product of Example 7 Step D. (29 mg), HATU (57 mg), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate, Aldrich Chemical Co.) and CH₂Cl₂ (5 mL) at 0°C was treated with diisopropylethylamine (.023 mL), and the mixture was stirred an additional

25

3 hr. at room temperature. The mixture was poured into ice-cold EtOAc

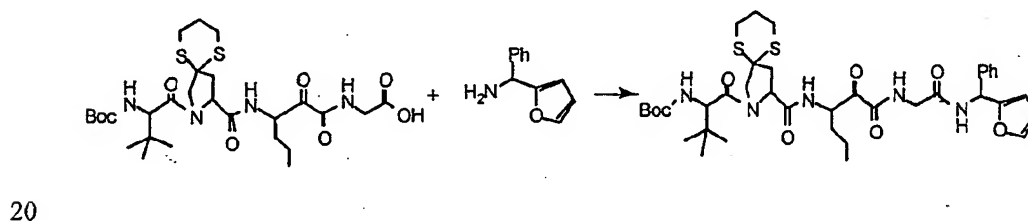
(50 mL) and washed successively with cold 5% aqueous K_2CO_3 , cold 0.1 N HCl, and brine. The extract was dried over anhydrous $MgSO_4$, the mixture was filtered, the filtrate was evaporated *in vacuo*, and the residue was chromatographed (silica gel, 1:1 EtOAc:CH₂Cl₂). The crude product was triturated under (*i*-Pr)₂O and filtered to leave the product as a white powder (81 mg), C₃₇H₅₂N₆O₇S₃ (789.04), LRMS (FAB) M+1 = 789.4.

Example 17

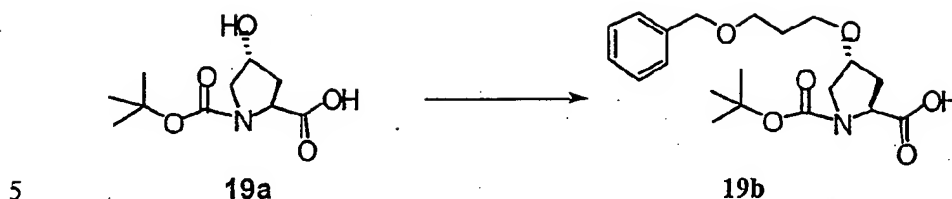


Following the procedure of Example of Example 16 Step C., the product of Example 16 Step B. was reacted with the product of Example 9 Step B. to obtain the corresponding product, C₃₈H₅₃N₅O₇S₃ (788.05),
15 LRMS (FAB) M+1 = 788.4.

Example 18



Following the procedure of Example of Example 16 Step C., the product of Example 16 Step B was reacted with the product of Example 9 Step B to obtain the corresponding product, C₃₈H₅₃N₅O₈S₂ (771.99), LRMS (FAB) M+1 = 772.4.

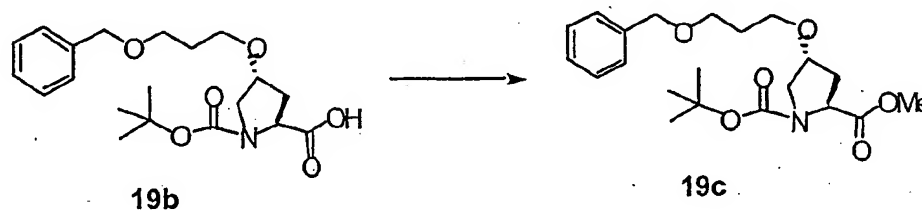
Example 19Step A:

To a solution of Boc-Hyp-OH (7.0 g, 30.3 mmol) and benzyl 3-bromopropyl ether (7.8 g, 34.0 mmol) in anhydrous DMF (400 mL) at room temperature was added sodium hydride (3.5 g, 60% dispersion in mineral oil, 87.5 mmol) and sodium iodide (0.5 g, 3.33 mmols) with stirring. The resulting suspension was vigorously stirred at room temperature overnight (18 h). The reaction was quenched carefully with a slow addition of water (50 mL) and acidified with 6 N HCl solution (20 mL). After addition of ethyl acetate (800 mL), brine (150 mL) and more water (150 mL), the formed two layers were separated and the organic layer was washed with 5% H₃PO₄ (3X200 mL). It was then dried with MgSO₄, filtered and concentrated in vacuo to afford **19b** as an oil which was used in Step B without further purification.

10

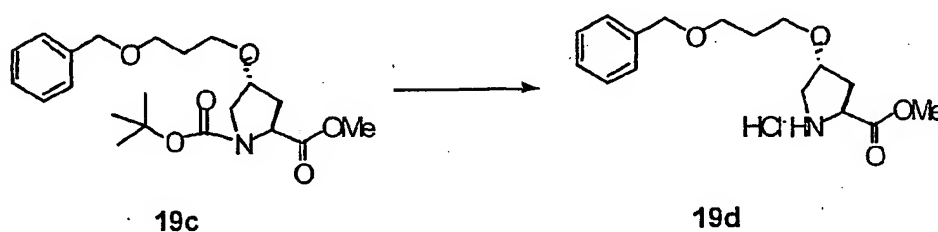
15

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Step B:

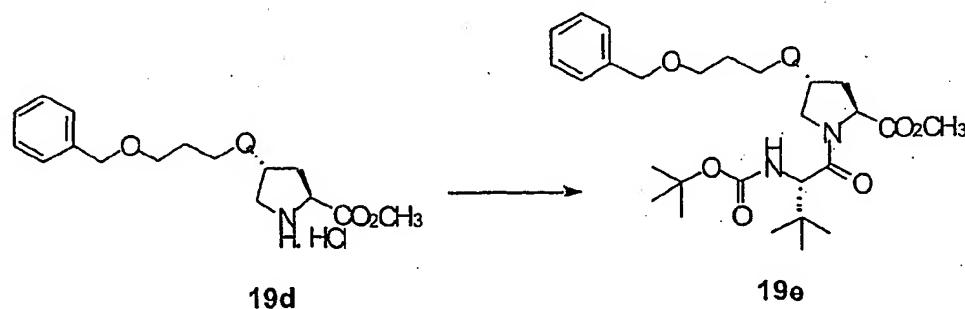
The acid **19b** from Step A was dissolved in benzene (25 mL) and methanol (28 mL). To this solution at room temperature was added a solution of trimethylsilyl diazomethane (27 mL, 2.0 M in cyclohexane) with caution. After being stirred at room temperature for 1 h, it was concentrated in vacuo to yield the methyl ester. Flash chromatography (8 to 20 % EtOAc-CH₂Cl₂) afforded **1c** (5.15 g; 13.1 mmol, 43%, 2 steps) as an oil.

Step C:



The Boc-amino methyl ester **19c** (5.83 g, 14.8 mmol) was dissolved in 4 N HCl in dioxane (80 mL, 320 mmol) and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC. After 5 h, the solution was concentrated in vacuo and the residue was kept under vacuum overnight to yield a white solid which was used in the next coupling reaction without further purification.

20 Step D



5

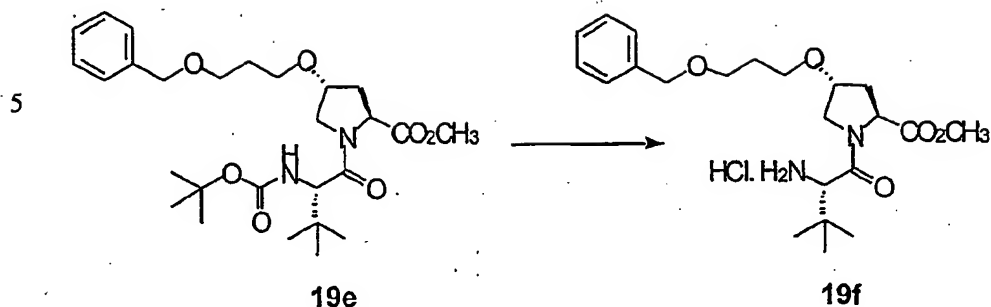
10

To a solution of the amine ester **19d** (from Step 19B), *N*-Boc-tertbutylglycines as coupling partners 14.9 mmol), HOObt (2.60 g, 15.9 mmol) and EDCI (3.41 g, 17.8 mmol) in anhydrous DMF (150 mL) and CH₂Cl₂ at -20°C, was added NMM (6.50 mL, 59.1 mmol). After being stirred at this temperature for 30 min, the reaction mixture was kept in a freezer overnight (18 h). It was then stirred in air and allowed to warm to room temperature in 1h. EtOAc (450 mL), brine (100 mL) and 5% H₃PO₄ (100 mL) were added. The separated organic solution was washed with 5% H₃PO₄ (100 mL), saturated aqueous sodium bicarbonate solution (2 X 150 mL), water (150 mL), and brine (150 mL), dried with magnesium sulfate, filtered and concentrated in vacuo.

The material of **19e** was purified by flash column chromatography using 90/10 dichloromethane/ethyl acetate to provide **12a** in 73% yield. ¹³C NMR (mixture of rotamers, CDCl₃) 26.20, 28.31, 29.07, 30.06, 34.94, 35.86, 37.06, 51.21, 52.16, 52.84, 57.78, 58.33, 65.95, 66.92, 72.97, 75.48, 79.45, 127.55, 127.66, 128.35, 138.45, 155.62, 165.06, 171.13, 172.54; HRMS (FAB) Calcd for C₂₇H₄₃N₂O₇: 507.3070 (M+H)⁺. Found: 507.3077.

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95

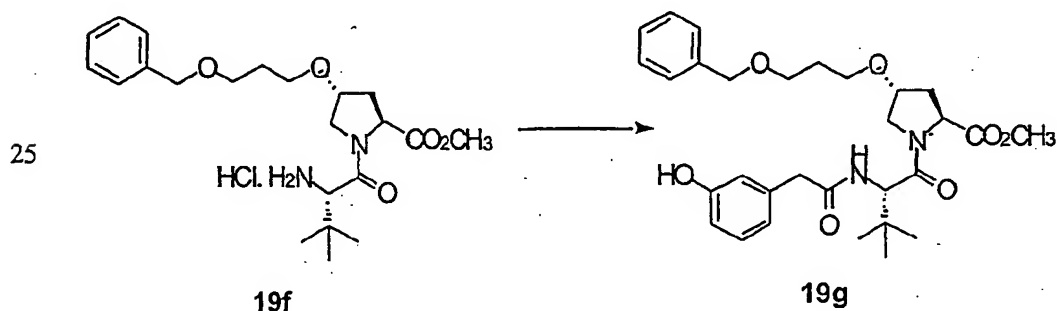
Step E:

The desired compound **19f** was prepared as follows

The Boc-amino methyl ester **19e** (6.53 g, 12.3 mmol) was dissolved in 4 N HCl (60 mL, 240 mmol) and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC.

15 After 4 h, the solution was concentrated in vacuo and the residue was kept under vacuum overnight to give a white solid which was used in the next coupling reaction without further purification. The material was carried forward to the next step.

20 Step F:



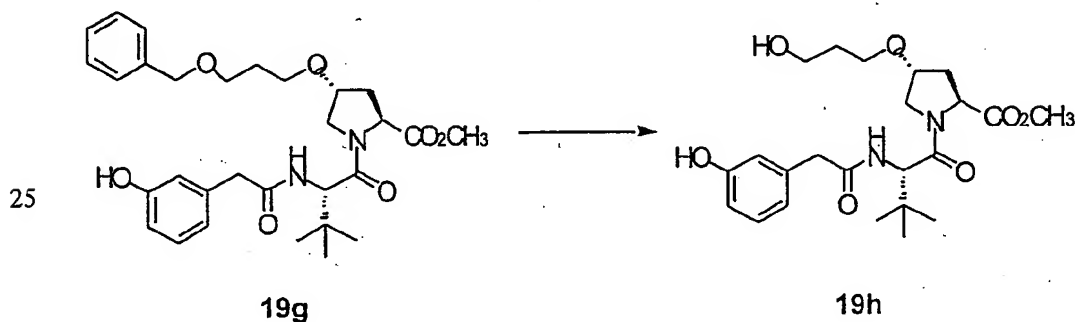
The desired product **19g** was prepared as follows:

To a solution of the amine **19f** (from Step 1D), 3-hydroxy phenylacetic acid (1.90 g, 12.5 mmol), HOObt (2.10 g, 12.9 mmol) and EDCI (2.85 g, 14.9 mmol) in anhydrous DMF (250 mL) and CH₂Cl₂ (100 mL) at -20°C, was added NMM (4.20 mL, 38.2 mmol). After being stirred at
5 this temperature for 30 min, the reaction mixture was kept in a freezer overnight (18 h). It was then stirred in air and allowed to warm to room temperature in 1h. EtOAc (500 mL), brine (100 mL) and 5% H₃PO₄ (100 mL) were added. The separated organic solution was washed with 5%
H₃PO₄ (100 mL), saturated aqueous sodium bicarbonate solution (2 X
10 150 mL), water (150 mL), and brine (150 mL), dried with magnesium sulfate, filtered and concentrated in vacuo.

The material was purified by flash column chromatography using 99/1 dichloromethane/methanol to yield **19g** in 91%. ¹³C NMR (CDCl₃) δ
26.24, 29.93, 34.95, 35.96, 43.48, 52.18, 53.09, 57.06, 58.06, 66.10,
15 66.92, 72.93, 77.43, 114.59, 116.14, 120.87, 127.58, 127.64, 127.74,
128.37, 130.02, 135.95, 138.39, 156.90, 170.65, 171.06, 172.38; HRMS (FAB) Calcd for C₃₀H₄₁N₂O₇: 541.2914 (M+H)⁺. Found: 541.2921.

Step G:

20



The desired product **19h** was prepared as follows:

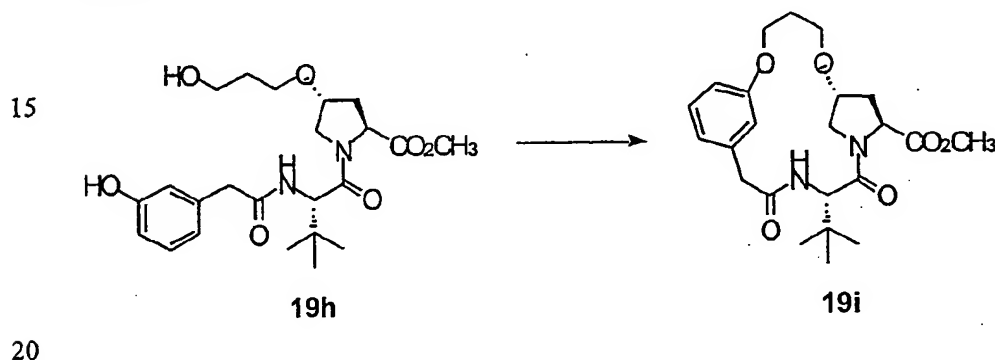
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To a solution of the benzyl ether **19g** (6.23 g, 11.0 mmol) in ethanol (200 mL) under nitrogen at room temperature was added 10 % Pd-C (1.5 g) cautiously. The resulting suspension was vigorously stirred at room temperature under hydrogen for 23 h.

5 The product **19h** obtained after filtering off the catalyst was pure enough for subsequent manipulations. ^{13}C NMR (CDCl_3) δ 26.27, 32.09, 35.44, 35.67, 43.19, 52.21, 52.74, 57.60, 58.21, 58.75, 65.78, 77.74, 114.74, 116.02, 120.68, 130.07, 135.66, 157.11, 170.59, 172.05, 172.51; HRMS (FAB) Calcd for $\text{C}_{23}\text{H}_{35}\text{N}_2\text{O}_7$: 451.2444 ($\text{M}+\text{H}$) $^+$. Found:
10 451.2436.

Step H:

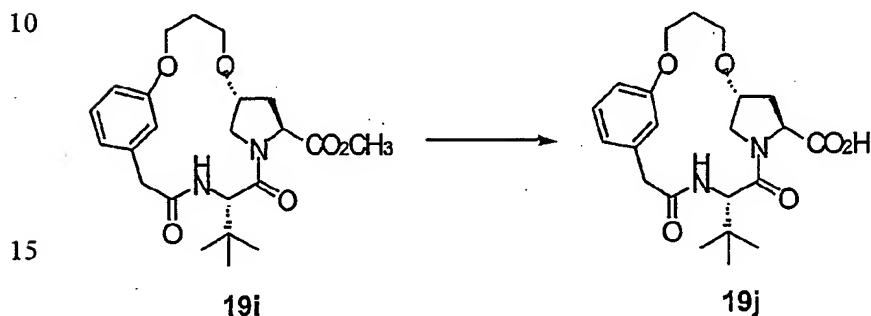


The desired product **19i** was prepared as follows:

25 A solution of the phenol alcohol (9.43 mmol) and ADDP (6.60 g, 26.2 mmol) in anhydrous CH_2Cl_2 was bubbled with argon through a frit glass bubbler for 20 min. To this solution at 0°C was added triphenylphosphine (4.10 g, 16.3 mmol). After stirring at 0°C for 20 min, a second portion of triphenylphosphine (3.40 g, 13.5 mmol) was added. The solution was then warmed to room temperature and stirred overnight (24
30 h) under nitrogen until TLC indicated the complete consumption of the starting material.

The crude material was suspended in ethyl acetate/hexane (approx. 1/1) and the undissolved solid material was filtered off. Repeated this process once again, the filtrate was concentrated and applied on the column as a dichloromethane solution. The column was eluted with 75/25
5 hexane/acetone to yield 29% of **19i**. HRMS (FAB) Calcd for $C_{23}H_{33}N_2O_6$: 433.2339 (M+H)⁺. Found: 433.2339.

Step I:



The desired compound **19j** was prepared as follows in quantitative yields:

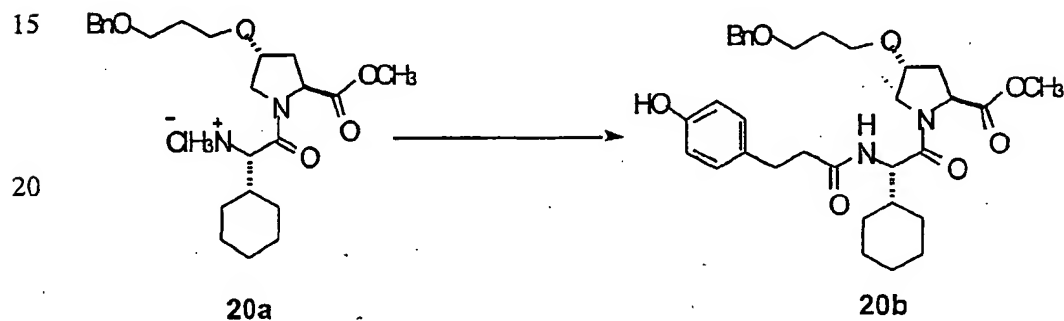
20 An aqueous lithium hydroxide solution (0.45 g in 30 mL H₂O) was added to a 0°C solution of the methyl ester **19j** in THF (30 mL) and methanol (30 mL). The mixture was stirred in an ice bath and warmed to room temperature along with it in 4 h. The progress of the reaction was monitored by TLC. After the volatiles were removed in vacuo, EtOAc (150
25 mL) and water (30 mL) were added and the two layers separated. The aqueous solution was extracted again with CH₂Cl₂ (150 mL), after which it was acidified to pH = 1. EtOAc (200 mL) was then added and the aqueous solution was saturated with solid sodium chloride. After separation of the layers, the aqueous layer was extracted with EtOAc (2 X 150 mL). Organic

solutions were combined, dried with magnesium sulfate, filtered and concentrated in vacuo to afford compound **19j**.

^1H NMR (DMSO- d_6) δ 0.96 (s, 9H), 1.66-1.70 (m, 1H), 1.75-1.82 (m, 2H), 2.43 (dd, 1H), 3.32-3.36 (m, 2H), 3.48-3.52 (m, 1H), 3.55 (dd, 1H), 3.84 (app. d, 1H), 3.99 (app. d, 1H), 4.06-4.10 (m, 3H), 4.16 (dd, 1H), 4.69 (d, 1H), 6.70-6.72 (m, 3H), 7.15 (app. t, 1H), 8.42 (d, 1H), 12.43 (br. s, 1H); ^{13}C NMR (DMSO- d_6) δ 26.25, 28.54, 33.31, 34.97, 41.22, 53.96, 56.11, 56.97, 63.36, 64.96, 76.84, 111.94, 115.25, 121.73, 129.13, 138.36, 158.27, 169.85, 170.15, 173.04; HRMS (FAB) Calcd for $\text{C}_{22}\text{H}_{31}\text{N}_2\text{O}_6$: 419.2182 (M+H) $^+$. Found: 419.2180.

Example 20

Step A



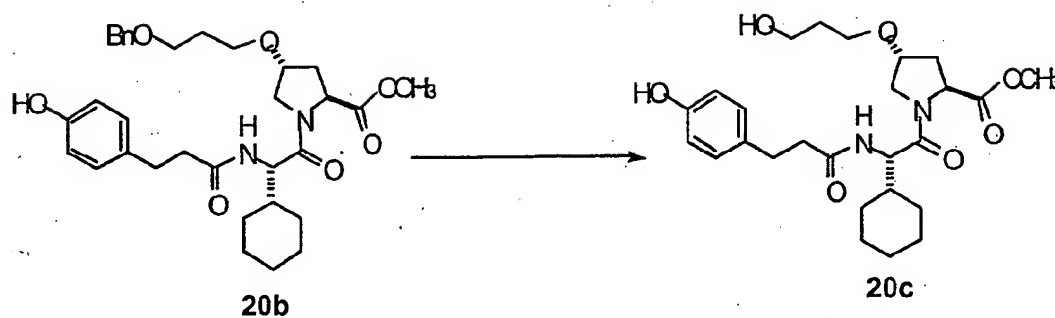
The compound **20a** was prepared as set forth in Scheme 9 referencing to Scheme 8.

The desired product **20b** was prepared as follows:

To a solution of the amine **20a**, 3-hydroxy phenylacetic acid (1.90 g, 12.5 mmol), HOObt (2.10 g, 12.9 mmol) and EDCI (2.85 g, 14.9 mmol) in anhydrous DMF (250 mL) and CH₂Cl₂ (100 mL) at -20°C, was added NMM (4.20 mL, 38.2 mmol). After being stirred at this temperature for 30 min, the reaction mixture was kept in a freezer overnight (18 h). It was then stirred in air and allowed to warm to room temperature in 1h. EtOAc (500 mL), brine (100 mL) and 5% H₃PO₄ (100 mL) were added. The separated organic solution was washed with 5% H₃PO₄ (100 mL), saturated aqueous sodium bicarbonate solution (2 X 150 mL), water (150 mL), and brine (150 mL), dried with magnesium sulfate, filtered and concentrated in vacuo.

The material was purified by flash column chromatography using EtOAc/Hex (7:3) to yield **64a** in 80%.; ¹H NMR (CDCl₃, δ) : 7.35-7.29 (m, 5 H), 7.02 (d, 2 H, J=8.4 Hz), 6.72 (d, 2 H, J= 6.9Hz) 6.01 (d, 1 H), 4.60 (t, 1 H), 4.52 (s, 1 H), 3.8-3.61(m, 2 H), 3.72 (s, 3 H), 3.54-3.51(m, 4 H), 2.83 (t, 2 H, J=7.5 Hz), 2.39 (t, 2 H, J= 8.1 Hz) 2.41-2.20 (m, 1 H), 2.05-1.83 (m, 1 H), 1.85-1.58 (m, 8 H), 1.26-1.24 (m, 5 H); ¹³C NMR (CDCl₃, δ): 172.2, 171.9, 171.0, 154.4, 138.3, 132.2, 129.4, 128.4, 127.7, 127.6, 115.4, 73.0, 66.9, 66.2, 57.9, 54.9, 52.5, 52.3, 41.0, 38.5, 34.7, 30.8, 30.0, 29.4, 27.9, 26.1, 26.0, 25.9.

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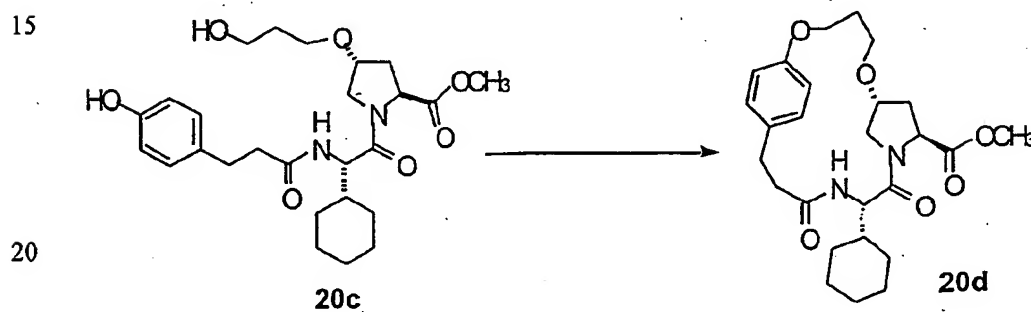
Step B

5

The desired product 20c was obtained as follows:

To a solution of 20c (11.0 mmol) in ethanol (200- ml) under nitrogen at room temperature was added 10% Pd/C (1.5g) cautiously. The resulting suspension was vigorously stirred at room temperature under hydrogen for 23h.

10

Step C

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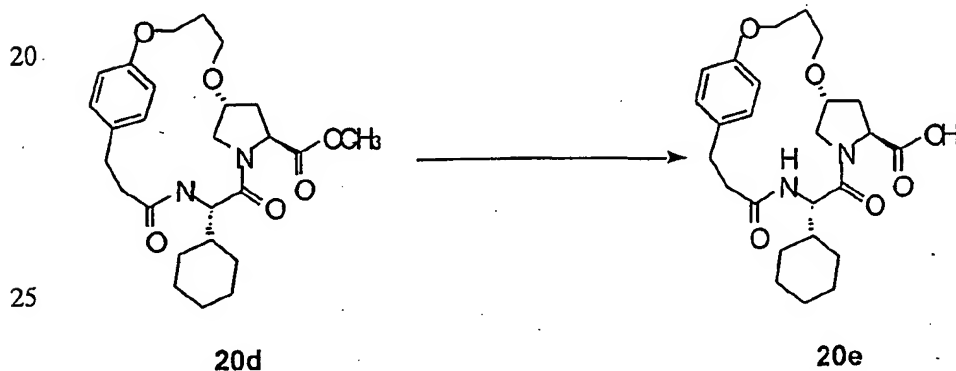
20

The desired product **20d** was obtained as follows:

A solution of **20d** (9.43 mmol) and ADDP (6.60g, 26.2 mmol) in anhydrous CH_2Cl_2 was bubbled with argon through a frit glass bubbler for 20 min. To this solution at 0°C was added triphenylphosphine (4.10g, 16.3 mmol). After stirring at 0°C for 20 min, a second portion of triphenylphosphine (3.40g, 13.5 mmol) was added. The solution was then warmed to room temperature and stirred overnight (24h) under nitrogen until TLC indicated the complete consumption of the starting material.

The crude reaction mixture was purified by SiO_2 gel chromatography (acetone/Hexanes 3:7) to yield **64c** (64 mg, 16%) as a colorless solid.; ^{13}C NMR (CDCl_3) δ 172.1, 171.1, 171.0, 157.7, 131.0, 129.9, 114.3, 78.1, 64.7, 63.3, 58.7, 55.3, 52.2, 52.0, 42.1, 37.9, 36.1, 30.8, 30.7, 29.7, 28.7, 28.5, 26.2, 26.0; MS (FAB) 473 ($\text{M}+1$)⁺, (100), 327 (20).

Step D

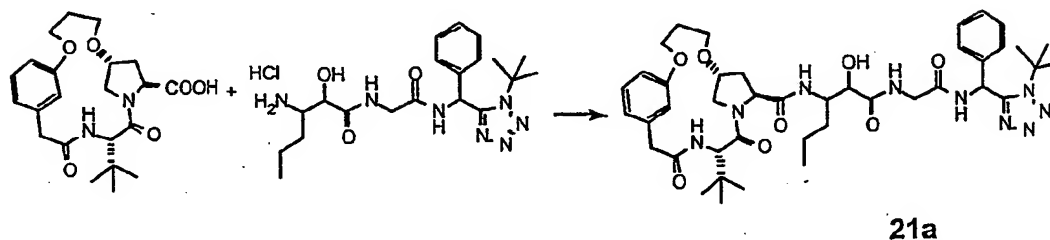


The acid **20e** was synthesized as follows:

An aqueous sodium hydroxide solution (0.45g in 30 ml H_2O) was added to a 0°C solution of compound **20e** in THF (30 ml) and methanol

(30 ml). This mixture was stirred in an ice bath and warmed to room temperature along with it in 4h. The progress of the reaction was monitored by TLC. After the volatiles were removed in vacuo, EtOAc (150 ml) and water (30 ml) were added and the two layers separated. The aqueous solution was saturated with solid sodium chloride. After separation of the layers, the aqueous layer was extracted with EtOAc (2 x 150 ml). Organic solutions were combined, dried with magnesium sulfate, filtered and concentrated in vacuo to afford compound 20e.

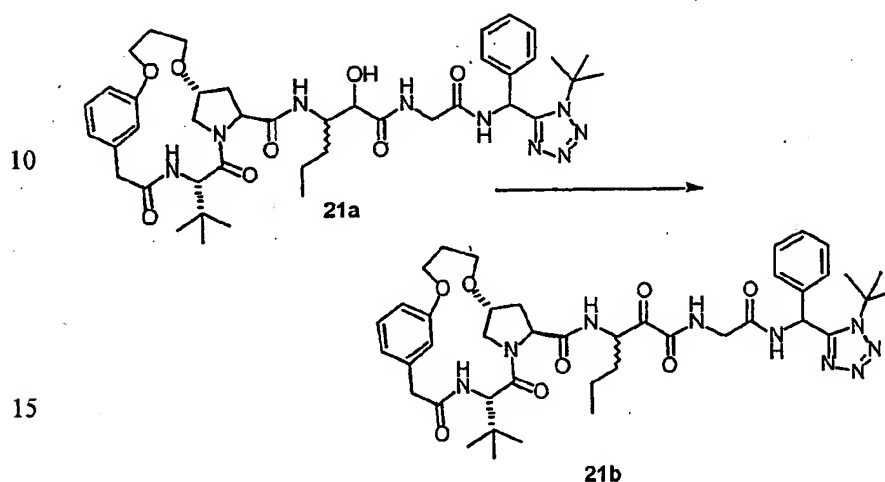
10 Example 21
Step A



A solution of the product of Example 19 (62 mg, 0.148 mmols) in dry DMF (2.5 mL) was treated with HOOBt (37 mg, 0.22 mmols) and NMM (58 mg, 0.592 mmols.) The reaction mixture was cooled to 0° C and treated with EDCI (63 mg, 0.33 mmols, 1.5 equiv) and stirred for 20 min. The reaction mixture was treated with the product of Example [11Q2] step B (74 mg, 0.016 mmols,) and stirred at rt for 48 h. The reaction mixture was concentrated in vacuo and diluted with H₂O (30 mL). The aqueous layer was extracted with CH₂Cl₂ (3x50 mL) and EtOAc(3x50 mL). The combined organic layers were extracted with aq. HCl (2M), aq. NaOH (2M), dried (Na₂SO₄) filtered concentrated in vacuo to obtain a colorless

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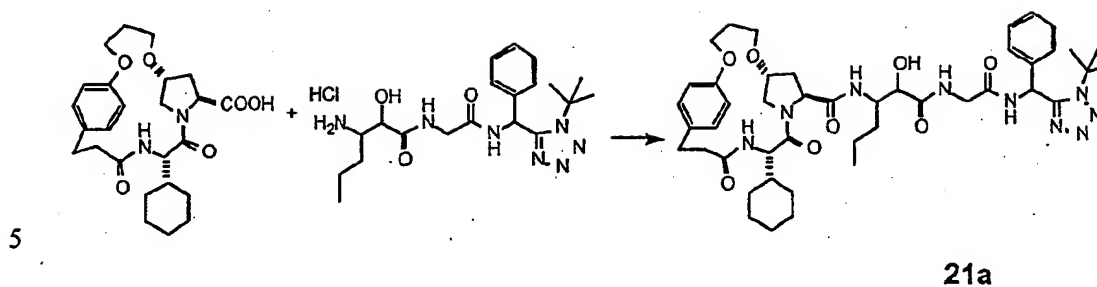
solid (120 mg) which was used for oxidation. MS: (Electron spray, m/z *rel int*): 818 $[(M+1)^+, 100]$.

5 Step B

A solution of the product of the preceding step (130 mg, 0.16 mmols) in CH_2Cl_2 (2.0 mL) was treated with Dess-Martin reagent (mg, 0.32 mmol, 2.0 equiv.). The reaction mixture was stirred at room temperature for 2 h and the mixture was concentrated in vacuo. The residue was purified by preparative TLC (SiO_2 , $\text{CH}_3\text{OH}/\text{CH}_2\text{Cl}_2$ 1:49) to yield oxidized product (55 mg, 42%) as a colorless solid. MS: (Electron spray, m/z *rel int*): 816 $[(M+1)^+, 100]$.

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Example 22
Step A

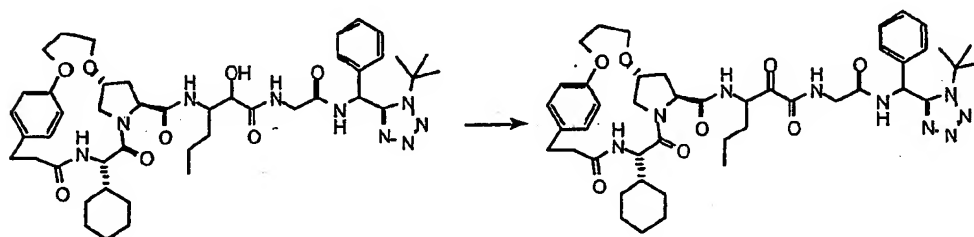


Following the procedure of Example 21 Step A, the product of Example 20, labeled 20e is reacted with the product of Example 13 Step B to afford the corresponding compound as a colorless solid product which was used for oxidation; MS: [electron spray, m/z (rel int)] 858 [(M+1)⁺, 100], 604 (10), 446 (10).

10

Example 23
Step B

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Following the procedure of Example 21 Step B., the product of the preceding Step was converted to the corresponding product as a colorless solid. MS: [electron spray, m/z (rel int)] 856 [(M+1)⁺, 100].

20

Assay for HCV Protease Inhibitory Activity:

Spectrophotometric Assay: Spectrophotometric assay for the HCV serine protease was performed on the inventive compounds by following the procedure described by R. Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, the disclosure of which is incorporated herein by reference. The assay based on the proteolysis of chromogenic ester substrates is suitable for the continuous monitoring of HCV NS3 protease activity. The substrates were derived from the P side of the NS5A-NS5B junction sequence (Ac-DTEDVVX(Nva), where X = A or P) whose C-terminal carboxyl groups were esterified with one of four different chromophoric alcohols (3- or 4-nitrophenol, 7-hydroxy-4-methyl-coumarin, or 4-phenylazophenol). Presented below are the synthesis, characterization and application of these novel spectrophotometric ester substrates to high throughput screening and detailed kinetic evaluation of HCV NS3 protease inhibitors.

Materials and Methods:

Materials: Chemical reagents for assay related buffers were obtained from Sigma Chemical Company (St. Louis, Missouri). Reagents for peptide synthesis were from Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) and Perseptive Biosystems (Framlingham, Massachusetts). Peptides were synthesized manually or on an automated ABI model 431A synthesizer (from Applied Biosystems). UV/VIS Spectrometer model LAMBDA 12 was from Perkin Elmer (Norwalk, Connecticut) and 96-well UV plates were obtained from Corning (Corning, New York). The prewarming block was from USA Scientific (Ocala, Florida) and the 96-well plate vortexer was from Labline Instruments (Melrose Park, Illinois). A Spectramax Plus microtiter plate reader with monochromator was obtained from Molecular Devices (Sunnyvale, California).

Enzyme Preparation: Recombinant heterodimeric HCV NS3/NS4A protease (strain 1a) was prepared by using the procedures published previously (D. L. Sali *et al*, *Biochemistry*, 37 (1998) 3392-3401). Protein concentrations were

determined by the Biorad dye method using recombinant HCV protease standards previously quantified by amino acid analysis. Prior to assay initiation, the enzyme storage buffer (50 mM sodium phosphate pH 8.0, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside and 10 mM DTT) was exchanged for the assay buffer (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 μ M EDTA and 5 μ M DTT) utilizing a Biorad Bio-Spin P-6 prepacked column.

Substrate Synthesis and Purification: The synthesis of the substrates was done as reported by R. Zhang *et al*, (*ibid.*) and was initiated by anchoring Fmoc-Nva-OH to 2-chlorotrityl chloride resin using a standard protocol (K. Barlos *et al*, *Int. J. Pept. Protein Res.*, 37 (1991), 513-520). The peptides were subsequently assembled, using Fmoc chemistry, either manually or on an automatic ABI model 431 peptide synthesizer. The N-acetylated and fully protected peptide fragments were cleaved from the resin either by 10% acetic acid (HOAc) and 10% trifluoroethanol (TFE) in dichloromethane (DCM) for 30 min, or by 2% trifluoroacetic acid (TFA) in DCM for 10 min. The combined filtrate and DCM wash was evaporated azeotropically (or repeatedly extracted by aqueous Na₂CO₃ solution) to remove the acid used in cleavage. The DCM phase was dried over Na₂SO₄ and evaporated.

The ester substrates were assembled using standard acid-alcohol coupling procedures (K. Holmber *et al*, *Acta Chem. Scand.*, B33 (1979) 410-412). Peptide fragments were dissolved in anhydrous pyridine (30-60 mg/ml) to which 10 molar equivalents of chromophore and a catalytic amount (0.1 eq.) of para-toluenesulfonic acid (pTSA) were added. Dicyclohexylcarbodiimide (DCC, 3 eq.) was added to initiate the coupling reactions. Product formation was monitored by HPLC and found to be complete following 12-72 hour reaction at room temperature. Pyridine solvent was evaporated under vacuum and further removed by azeotropic evaporation with toluene. The peptide ester was deprotected with 95% TFA in DCM for two hours and extracted three times with anhydrous ethyl ether to remove excess chromophore. The deprotected substrate was purified by reversed phase HPLC on a C3 or C8 column with a 30% to 60% acetonitrile gradient (using six column volumes). The overall yield following HPLC purification

was approximately 20-30%. The molecular mass was confirmed by electrospray ionization mass spectroscopy. The substrates were stored in dry powder form under desiccation.

Spectra of Substrates and Products: Spectra of substrates and the corresponding
5 chromophore products were obtained in the pH 6.5 assay buffer. Extinction coefficients were determined at the optimal off-peak wavelength in 1-cm cuvettes (340 nm for 3-Np and HMC, 370 nm for PAP and 400 nm for 4-Np) using multiple dilutions. The optimal off-peak wavelength was defined as that wavelength yielding the maximum fractional difference in absorbance between substrate and
10 product (product OD - substrate OD)/substrate OD).

Protease Assay: HCV protease assays were performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate. Assay buffer conditions (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) were optimized for the NS3/NS4A heterodimer (D. L. Sali *et al, ibid.*)).
15 Typically, 150 µl mixtures of buffer, substrate and inhibitor were placed in wells (final concentration of DMSO 4 % v/v) and allowed to preincubate at 30 °C for approximately 3 minutes. Fifty µls of prewarmed protease (12 nM, 30°C) in assay buffer, was then used to initiate the reaction (final volume 200 µl). The plates were monitored over the length of the assay (60 minutes) for change in absorbance at
20 the appropriate wavelength (340 nm for 3-Np and HMC, 370 nm for PAP, and 400 nm for 4-Np) using a Spectromax Plus microtiter plate reader equipped with a monochromator (acceptable results can be obtained with plate readers that utilize cutoff filters). Proteolytic cleavage of the ester linkage between the Nva and the chromophore was monitored at the appropriate wavelength against a no enzyme
25 blank as a control for non-enzymatic hydrolysis. The evaluation of substrate kinetic parameters was performed over a 30-fold substrate concentration range (~6-200 µM). Initial velocities were determined using linear regression and kinetic constants were obtained by fitting the data to the Michaelis-Menten equation using non-linear regression analysis (Mac Curve Fit 1.1, K. Raner). Turnover numbers
30 (k_{cat}) were calculated assuming the enzyme was fully active.

Evaluation of Inhibitors and Inactivators: The inhibition constants (K_i) for the competitive inhibitors of Table A were determined experimentally at fixed concentrations of enzyme and substrate by plotting v_o/v_i vs. inhibitor concentration ($[I]_o$) according to the rearranged Michaelis-Menten equation for competitive inhibition kinetics: $v_o/v_i = 1 + [I]_o / (K_i (1 + [S]_o / K_m))$, where v_o is the uninhibited initial velocity, v_i is the initial velocity in the presence of inhibitor at any given inhibitor concentration ($[I]_o$) and $[S]_o$ is the substrate concentration used. The resulting data were fitted using linear regression and the resulting slope, $1/(K_i(1+[S]_o/K_m))$, was used to calculate the K_i value.

10 The obtained K_i values for various compounds of the present invention are given in the afore-mentioned Table wherein the compounds have been arranged in the order of ranges of K_i values. From these test results, it would be apparent to the skilled artisan that the compounds of the invention have excellent utility as NS3-serine protease inhibitors.

15 While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

20

Table A - Serine Protease Inhibitory Activity

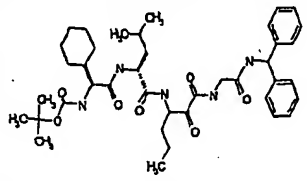
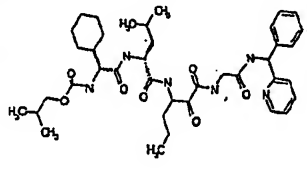
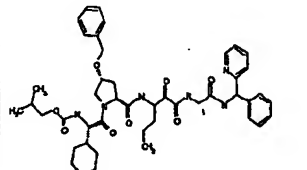
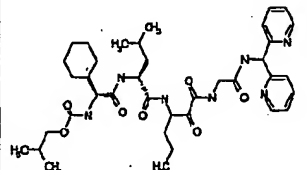
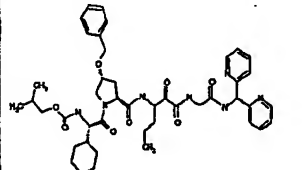
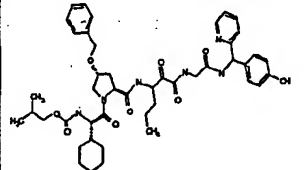
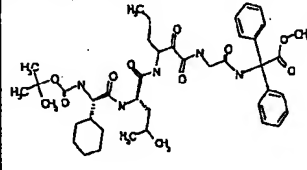
Ex.	structure	MolWt.	HCV Assay Range
			Ki* (nM)
I		719.93	d
II		720.92	c
III		811.00	b
IV		721.90	c
V		811.99	b
VI		827.00	c
VII		777.97	c

Table A - Serine Protease Inhibitory Activity

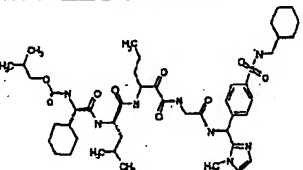
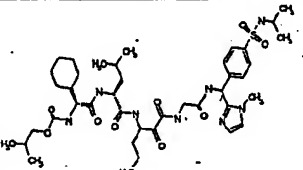
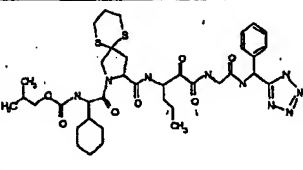
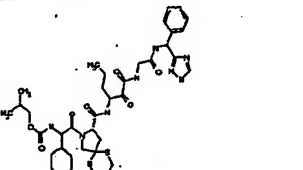
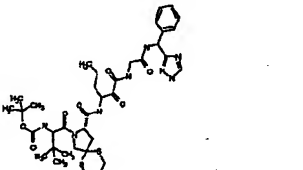
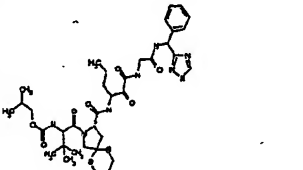
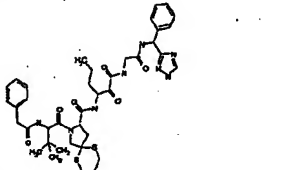
Ex.	structure	MolWt.	HCV Assay Range
			Ki* (nM)
VIII		899.17	d
IX		845.08	c
X		800.02	a
XI		799.03	b
XII		772.99	a
XIII		772.99	b
XIV		791.01	b

Table A - Serine Protease Inhibitory Activity

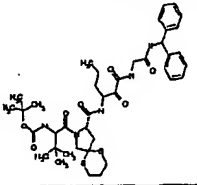
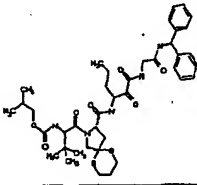
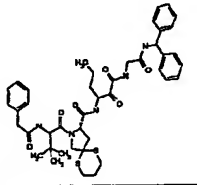
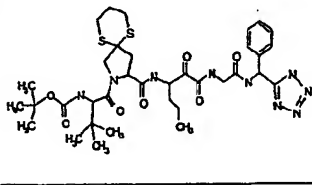
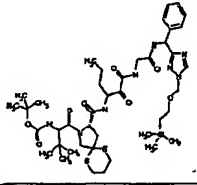
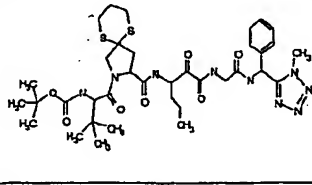
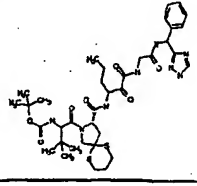
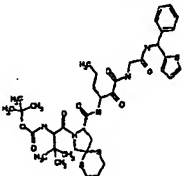
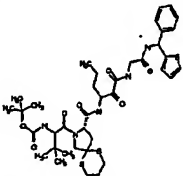
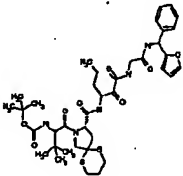
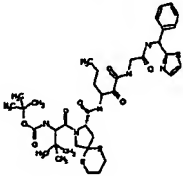
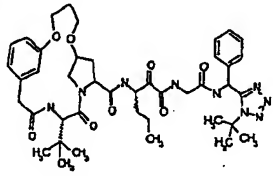
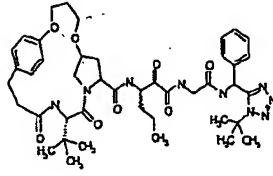
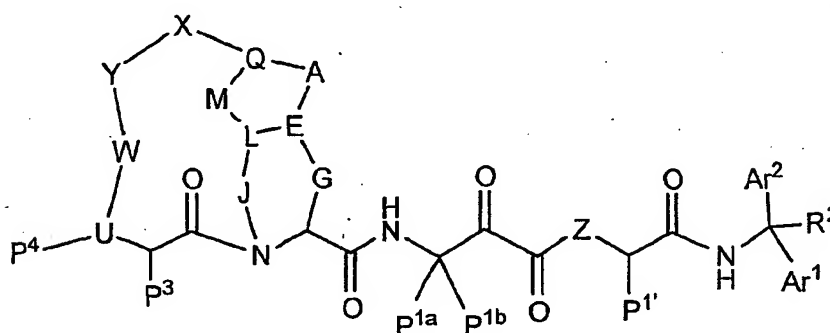
Ex.	structure	MolWt.	HCV Assay Range
			Ki* (nM)
XV		782.04	b
XVI		782.04	b
XVII		800.06	b
XVIII		773.98	b
XIX		903.26	c
XX		788.01	b
XXI		772.99	a

Table A - Serine Protease Inhibitory Activity

		HCV Assay Range	
Ex.	structure	MolWt.	Ki* (nM)
XXII		788.07	b
XXIII		788.07	c
XXIV		772.00	b
XXV		789.05	b
XXVI		815.98	b
XXVII		830.01	c
HCV Assay Ki* range: Category a=10-99nM; b=100-999nM; c=1000-9999nM; d=10,000-50,000nM			

WHAT IS CLAIMED IS:

1. A compound, including enantiomers, stereoisomers, rotomers and tautomers of said compound, and pharmaceutically acceptable salts, solvates or derivatives thereof, with said compound having the general structure shown in Formula I:



Formula I

- 10 wherein:

X and Y are independently selected from the moieties: alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyl ether, alkyl-aryl ether, aryl ether, alkyl amino, aryl amino, alkyl-aryl amino, alkyl thio, alkyl-aryl thio, aryl thio, alkyl sulfone, alkyl-aryl sulfone, aryl sulfone, alkyl-alkyl sulfoxide, alkyl-aryl sulfoxide, alkyl amide, alkyl-aryl amide, aryl amide, alkyl sulfonamide, alkyl-aryl sulfonamide, aryl sulfonamide, alkyl urea, alkyl-aryl urea, aryl urea, alkyl carbamate, alkyl-aryl carbamate, aryl carbamate, alkyl-hydrazide, alkyl-aryl hydrazide, alkyl hydroxamide, alkyl-aryl hydroxamide, alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl or a combination thereof, with the proviso that X and Y may optionally be additionally substituted with X^{11} or X^{12} :

X^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, with the proviso that X^{11} may be additionally optionally substituted with X^{12} ;

- 5 X^{12} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro, with the proviso that said alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from X^{12} ;
- 10

W may be present or absent, and if W is present, W is selected from C=O, C=S, or SO₂;

- Q may be present or absent, and when Q is present, Q is CH, N, P, (CH₂)_p, (CHR)_p, (CRR')_p, O, RNR, S, or SO₂; and when Q is absent, M is also absent, A is directly linked to X;
- 15

A is O, CH₂, (CHR)_p, (CHR-CHR')_p, (CRR')_p, NR, S, SO₂ or a bond;

U is selected from O, N, or CH;

E is CH, N or CR, or a double bond towards A, L or G;

- G may be present or absent, and when G is present, G is (CH₂)_p, (CHR)_p, or (CRR')_p; and when G is absent, J is present and E is directly connected to the carbon atom where G was connected to;
- 20

J may be absent or present, and when J is present, J is (CH₂)_p, (CHR)_p, or (CRR')_p, SO₂, NH, NR or O; and when J is absent, G is present and L is directly linked to nitrogen;

- 25 L may be present or absent, and when L is present, L is CH, CR, O, S or NR; and when L is absent, then M may be absent or present, and if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

- M may be present or absent, and when M is present, M is O, NR, S, SO₂, (CH₂)_p, (CHR)_p, (CHR-CHR')_p, or (CRR')_p;
- 30

p is a number from 0 to 6;

- R and R' are independently selected from the group consisting of H; C1-C10 alkyl; C2-C10 alkenyl; C3- C8 cycloalkyl; C3-C8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, cyano, nitro; (cycloalkyl)-
- 5 alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl; with said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl
- 10 moieties may be optionally substituted, with said term "substituted" – referring to optional and suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, cyano, nitro, sulfonamido; and
- 15 P^{1a}, P^{1b}, P^{1'} and P³ are independently selected from:
- H, C1-C10 straight or branched chain alkyl, C2-C10 straight or branched chain alkenyl, and C3-C8 cycloalkyl, C3-C8 heterocyclic; (cycloalkyl)alkyl or (heterocyclyl)alkyl , wherein said cycloalkyl is made up of 3 to 8 carbon atoms, and zero to 6 oxygen, nitrogen, sulfur, or phosphorus atoms, and
- 20 said alkyl is of 1 to 6 carbon atoms;
- aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein said alkyl is of 1 to 6 carbon atoms;
- wherein said alkyl, alkenyl, cycloalkyl, heterocyclyl; (cycloalkyl)alkyl and (heterocyclyl)alkyl moieties may be optionally substituted with R", and
- 25 further wherein said P^{1a} and P^{1b} may optionally be joined to each other to form a spirocyclic or spiroheterocyclic ring, with said spirocyclic or spiroheterocyclic ring containing zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and may be additionally optionally substituted with R";
- R" is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino,
- 30 arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido,

carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from Rⁿ;

5 Z is O, NH or NR^m;

R^m is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that R^m may be additionally optionally substituted with Rⁿ;

10 Ar¹ and Ar² are independently selected from phenyl; 2-pyridyl, 3-pyridyl, 4-pyridyl or their corresponding N-oxides; 2-thiophenyl; 3-thiophenyl; 2-furanyl; 3-furanyl; 2-pyrrolyl; 3-pyrrolyl; 2-imidazolyl; 3(4)-imidazolyl; 3-(1,2,4-triazolyl); 5-tetrazolyl; 2-thiazolyl; 4-thiazolyl; 2-oxazolyl; or 4-oxazolyl; either or both of which may be optionally substituted with R¹;

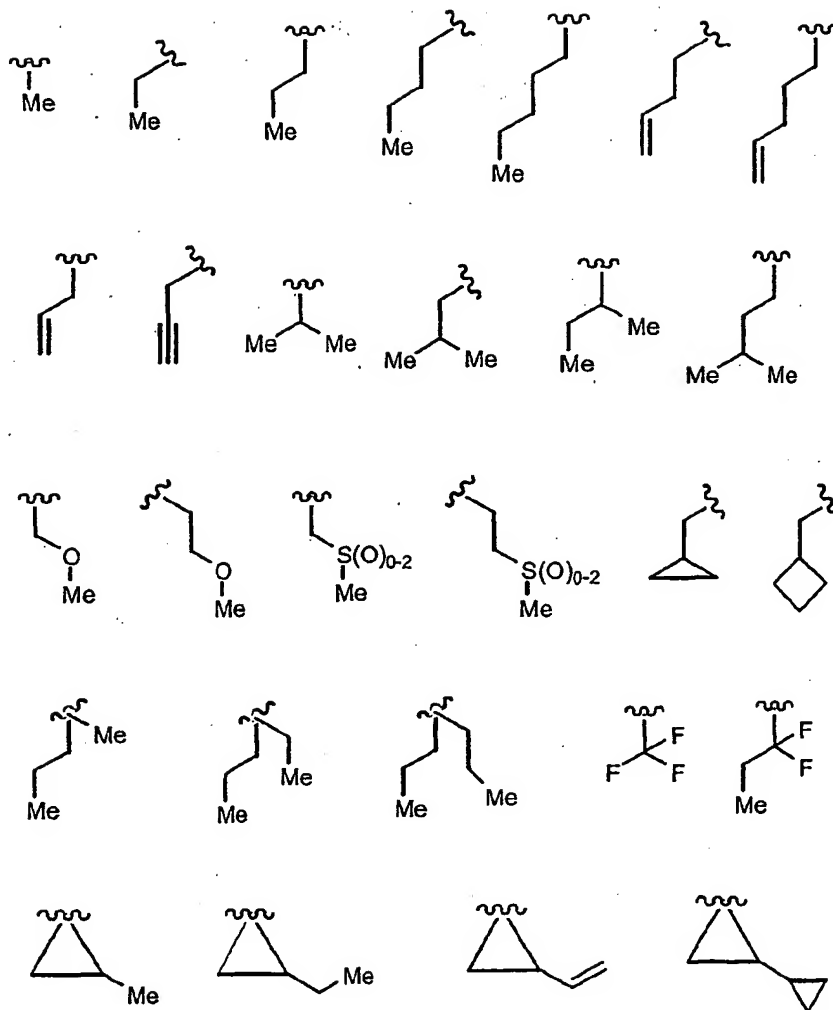
15 R¹ is H, halogen, cyano, nitro, CF₃, Si(alkyl)₃, straight-chain or branched lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl, hydroxy, alkoxy, aryloxy, alkoxycarbonyloxy, (alkylamino)carbonyloxy, mercapto, alkylthio, arylthio, alkylsulfinyl, heterocyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, amino, alkylamino, arylamino, alkylsulfonamide, arylsulfonamide, alkoxycarbonbylamino, alkylureido, or arylureido;

25 P⁴ is H, linear or branched alkyl, arylalkyl or aryl; and

R² is H, cyano, CF₃, straight-chain or branched lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylsulfonyl, arylsulfonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, alkylaminocarbonyl, (alkylamino)carbonyl, or arylaminocarbonyl.

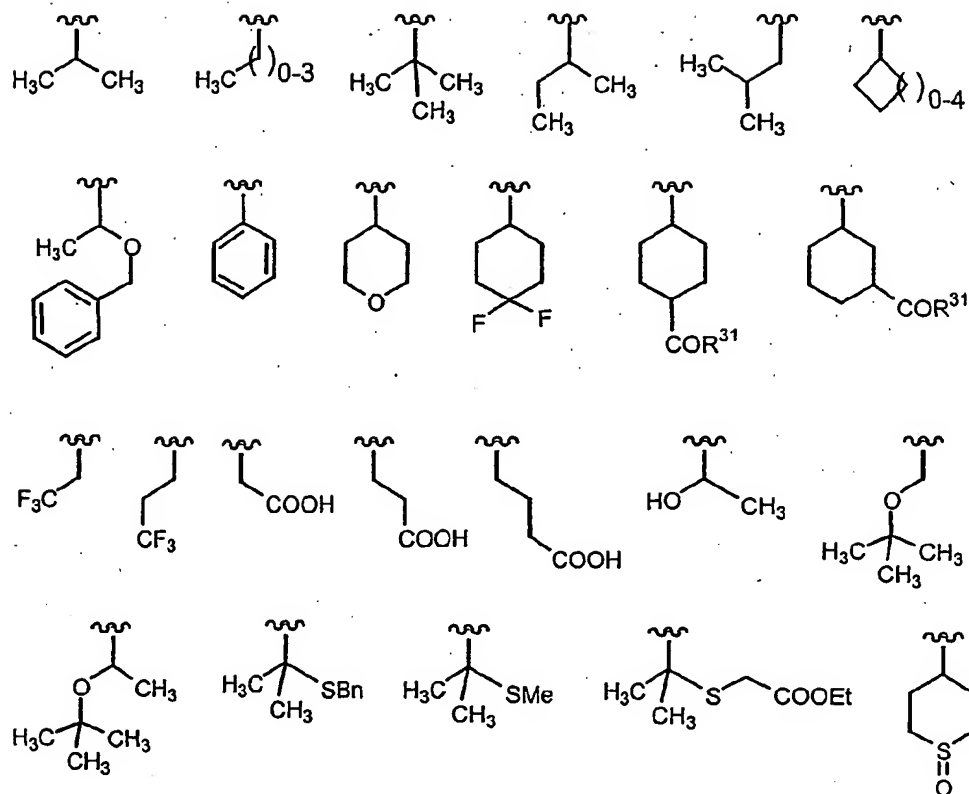
2. The compound according to Claim 1, wherein R^{21} is selected from the group consisting of H, alkyl, alkenyl, alkoxycarbonyl, or (allylamino) carbonyl.
3. The compound according to Claim 2, wherein R^{21} is H, U is N and
5 P^4 is H.
4. The compound according to Claim 1, wherein Ar^1 and Ar^2 are independently selected from the group consisting of phenyl, 2-thiophenyl, 2-furanyl, 3-furanyl, 3(4)-imidazolyl, 3-(1,2,4-triazolyl), 5-tetrazolyl, or 2-thiazolyl.
- 10 5. The compound according to Claim 4, wherein Ar^2 is phenyl and Ar^1 is selected from the group consisting of 3-(1,2,4-triazolyl), 5-tetrazolyl, or 2-thiazolyl and U is N and P^4 is H.
6. The compound according to Claim 1 or Claim 4, wherein R^1 is H, CF_3 , CH_3 , alkyl or alkenyl.
- 15 7. The compound according to Claim 4, wherein R^1 is H, CF_3 , CH_3 , alkyl or alkenyl.
8. The compound according to Claim 1, wherein P^{11} is either H or CH_3 .
9. The compound according to Claim 1, wherein P^{11} is H such that P^{11}
20 and the adjacent nitrogen and carbonyl moieties correspond to the residuum of a glycine unit.
10. The compound of Claim 4, wherein P^{1a} and P^{1b} are independently selected from the group consisting of the following moieties:

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- 5 11. The compound according to Claim 4, wherein P³ is selected from the group consisting of:

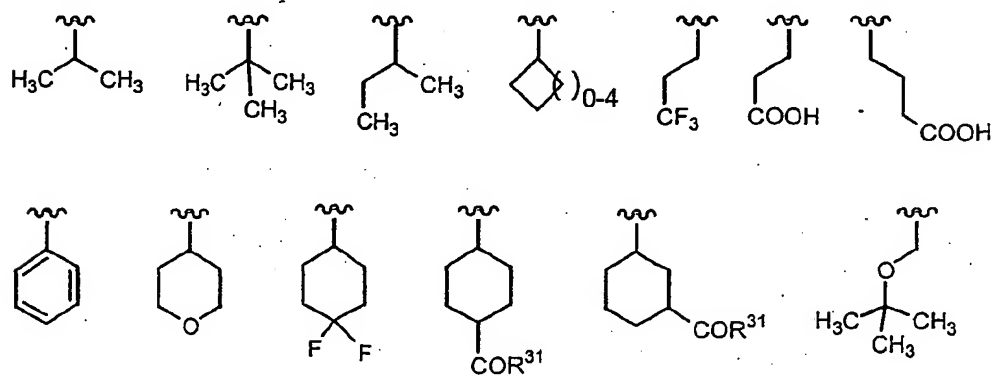
120



wherein $R^{31} = OH$ or O-alkyl.

12. The compound of Claim 4, wherein P^3 is selected from the group

5 consisting of the following moieties:



wherein $R^{31} = OH$ or O-alkyl.

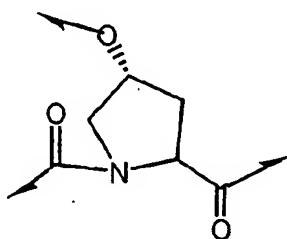
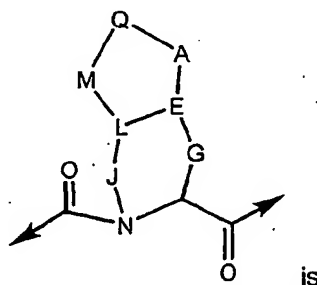
121

13. The compound according to Claim 1, wherein P^4 is selected from the group consisting of H, tertiary butyl, isobutyl and phenyl substituents.

14. The compound according to Claim 11, where Z is NH and U is N.

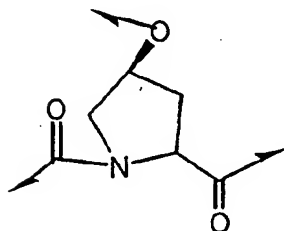
15. The compound of Claim 1, wherein the moiety:

5



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or

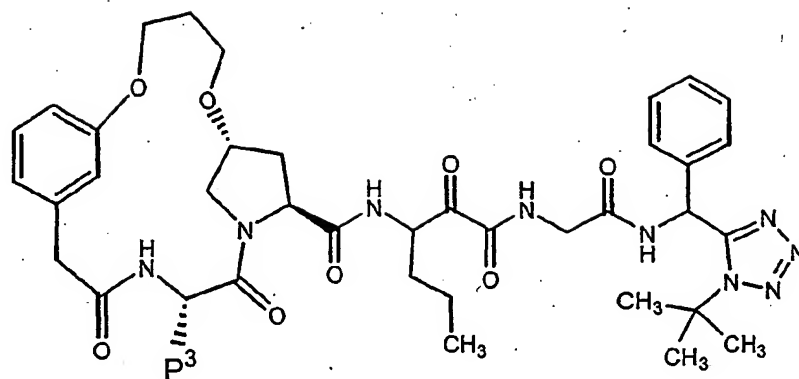


16. The compound of Claim 16, wherein Z is NH and U is N.

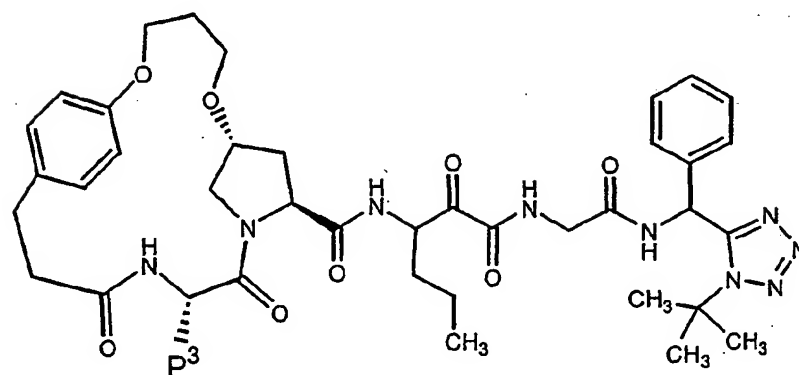
17. The compound according to Claim 1, wherein said compound is selected from the group consisting of compounds having the structural

15 formulae:

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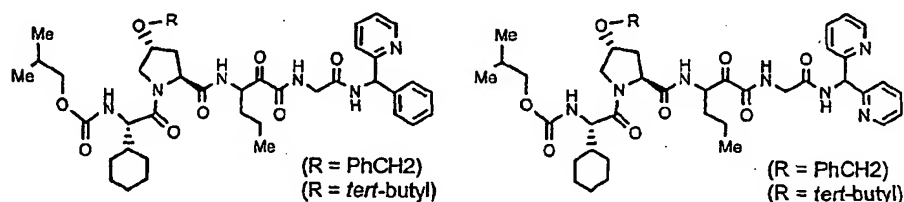
or



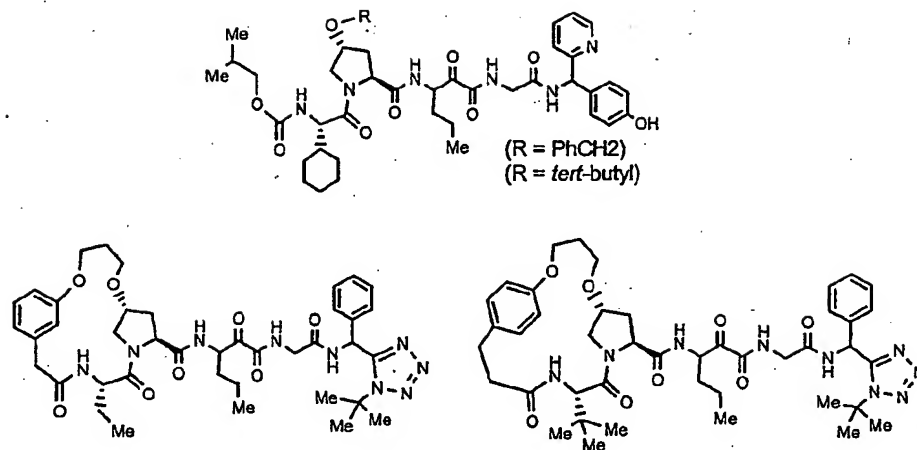
wherein P³ is an isopropyl, tertiary butyl, cyclopentyl, or cyclohexyl moiety.

- 5 18. A pharmaceutical composition comprising as an active ingredient a compound of Claim 1.
19. The pharmaceutical composition of Claim 18 for use in treating disorders associated with HCV.
20. The pharmaceutical composition of Claim 18, additionally
- 10 comprising a pharmaceutically acceptable carrier.
21. The pharmaceutical composition of Claim 20, additionally containing an antiviral agent.
22. The pharmaceutical composition of Claim 21, still additionally containing an interferon.
- 15 23. The pharmaceutical composition of Claim 22, wherein said antiviral agent is ribavirin and said interferon is α -interferon.

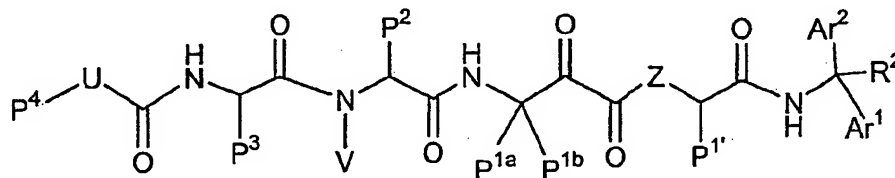
24. A method of treating disorders associated with the HCV virus, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of a compound of Claim 1.
- 5 25. The method of Claim 24, wherein said administration is subcutaneous.
26. The use of a compound of Claim 1 for the manufacture of a medicament to treat disorders associated with the HCV protease.
27. A method of preparing a pharmaceutical composition for treating
10 the disorders associated with the HCV virus, said method comprising bringing into intimate contact a compound of Claim 1 and a pharmaceutically acceptable carrier.
28. A compound exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and
15 pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:



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29. A compound, including enantiomers, stereoisomers, rotomers and tautomers of said compound, and pharmaceutically acceptable salts, solvates or derivatives thereof, with said compound having the general structure shown in Formula II:



Formula II

wherein:

- 10 P^{1a}, P^{1b}, P¹, P², and P³ are independently:
H, C1-C10 straight or branched chain alkyl, C2-C10 straight or branched chain alkenyl, and C3-C8 cycloalkyl, C3-C8 heterocyclic; (cycloalkyl)alkyl or (heterocyclyl)alkyl, wherein said cycloalkyl is made up of 3 to 8 carbon atoms, and zero to 6 oxygen, nitrogen, sulfur, or phosphorus atoms, and
- 15 said alkyl is of 1 to 6 carbon atoms;
aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein said alkyl is of 1 to 6 carbon atoms;
wherein said alkyl, alkenyl, cycloalkyl, heterocyclyl; (cycloalkyl)alkyl and (heterocyclyl)alkyl moieties may be optionally substituted with R", and

- further wherein said P^{1a} and P^{1b} may optionally be joined to each other to form a spirocyclic or spiroheterocyclic ring, with said spirocyclic or spiroheterocyclic ring containing zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and may be additionally optionally substituted with Rⁿ;
- 5 Rⁿ is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy, and aryl may be additionally
- 10 optionally substituted with moieties independently selected from R^m;
Z is O, NH or NR^m;
R^m is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that R^m may be additionally
- 15 optionally substituted with Rⁿ;
Ar¹ and Ar² are independently selected from phenyl; 2-pyridyl, 3-pyridyl, 4-pyridyl or their corresponding N-oxides; 2-thiophenyl; 3-thiophenyl; 2-furanyl; 3-furanyl; 2-pyrrolyl; 3-pyrrolyl; 2-imidazolyl; 3(4)-imidazolyl; 3-(1,2,4-triazolyl); 5-tetrazolyl; 2-thiazolyl; 4-thiazolyl; 2-oxazolyl; or 4-
- 20 oxazolyl; either or both of which may be optionally substituted with R¹;
R¹ is H, halogen, cyano, nitro, CF₃, Si(alkyl)₃, straight-chain or branched lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl, hydroxy, alkoxy, aryloxy, alkoxycarbonyloxy, (alkylamino)carbonyloxy, mercapto, alkylthio, arylthio, alkylsulfinyl, heterocyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylsulfonyl, heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, arylcarbonyl, carboxy, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, amino, alkylamino, arylamino, alkylsulfonamide, arylsulfonamide,
- 25 alkoxycarbonbylamino, alkylureido, or arylureido;
- 30

P⁴ is H, linear or branched alkyl, arylalkyl or aryl;

R² is H, cyano, CF₃, straight-chain or branched lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylsulfonyl, arylsulfonyl, carboxy, alkoxycarbonyl, aryloxy carbonyl,

5 alkylaminocarbonyl, (allylamino)carbonyl, or arylaminocarbonyl;

U is O, NH, CH₂ or CHRⁿ; and

V is H, methyl, or lower alkyl.

30. The compound according to Claim 29, wherein R² is selected from the group consisting of H, alkyl, alkenyl, alkoxycarbonyl, and (allylamino) carbonyl.

31. The compound according to Claim 30, wherein R² is H.

32. The compound according to Claim 31, wherein Ar¹ and Ar² are independently selected from the group consisting of phenyl, 2-thiophenyl, 2-furanyl, 3-furanyl, 3(4)-imidazolyl, 3-(1,2,4-triazolyl), 5-tetrazolyl, or 2-thiazolyl.

33. The compound according to Claim 32, wherein Ar² is phenyl and Ar¹ is selected from the group consisting of 3-(1,2,4-triazolyl), 5-tetrazolyl, or 2-thiazolyl.

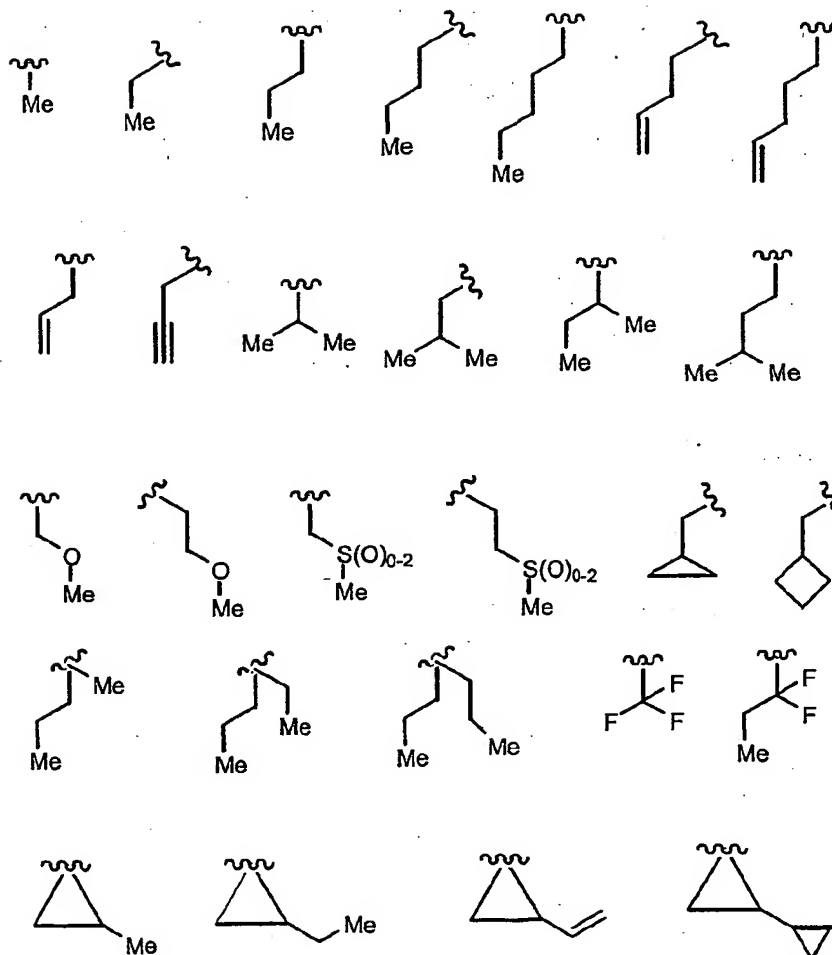
34. The compound according to Claim 29, R¹ is H, CF₃, CH₃, alkyl or alkenyl.

35. The compound according to Claim 29, wherein P¹ is selected either H or CH₃.

36. The compound according to Claim 29, wherein P¹ is H such that P¹ and the adjacent nitrogen and carbonyl moieties correspond to the residuum of glycine unit.

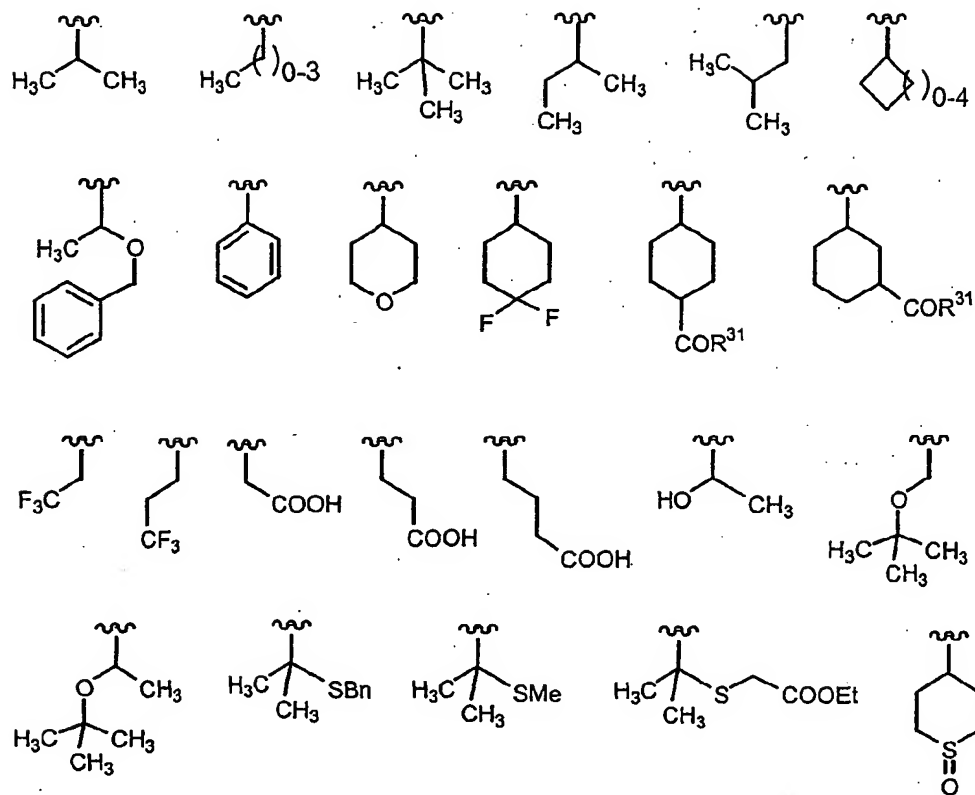
37. The compound of Claim 29, wherein P^{1a} and P^{1b} are independently selected from the group consisting of the following moieties:

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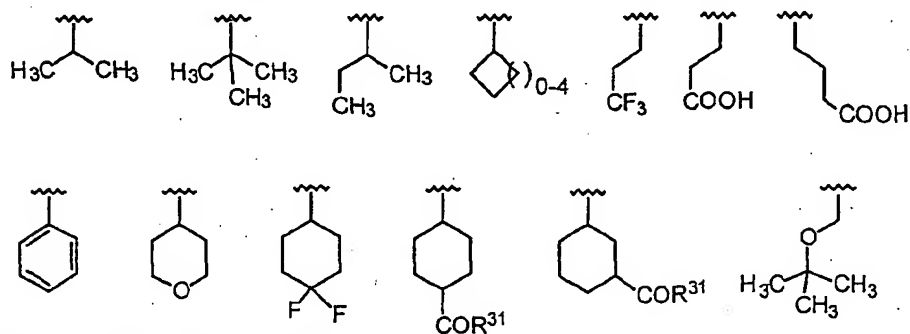
38. The compound according to Claim 29, wherein P³ is selected from the group consisting of:

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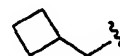
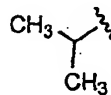
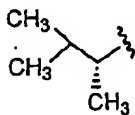
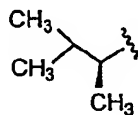
wherein $R^{31} = \text{OH}$ or O-alkyl.

- 5 39. The compound of Claim 38, wherein R^3 is selected from the group consisting of the following moieties:

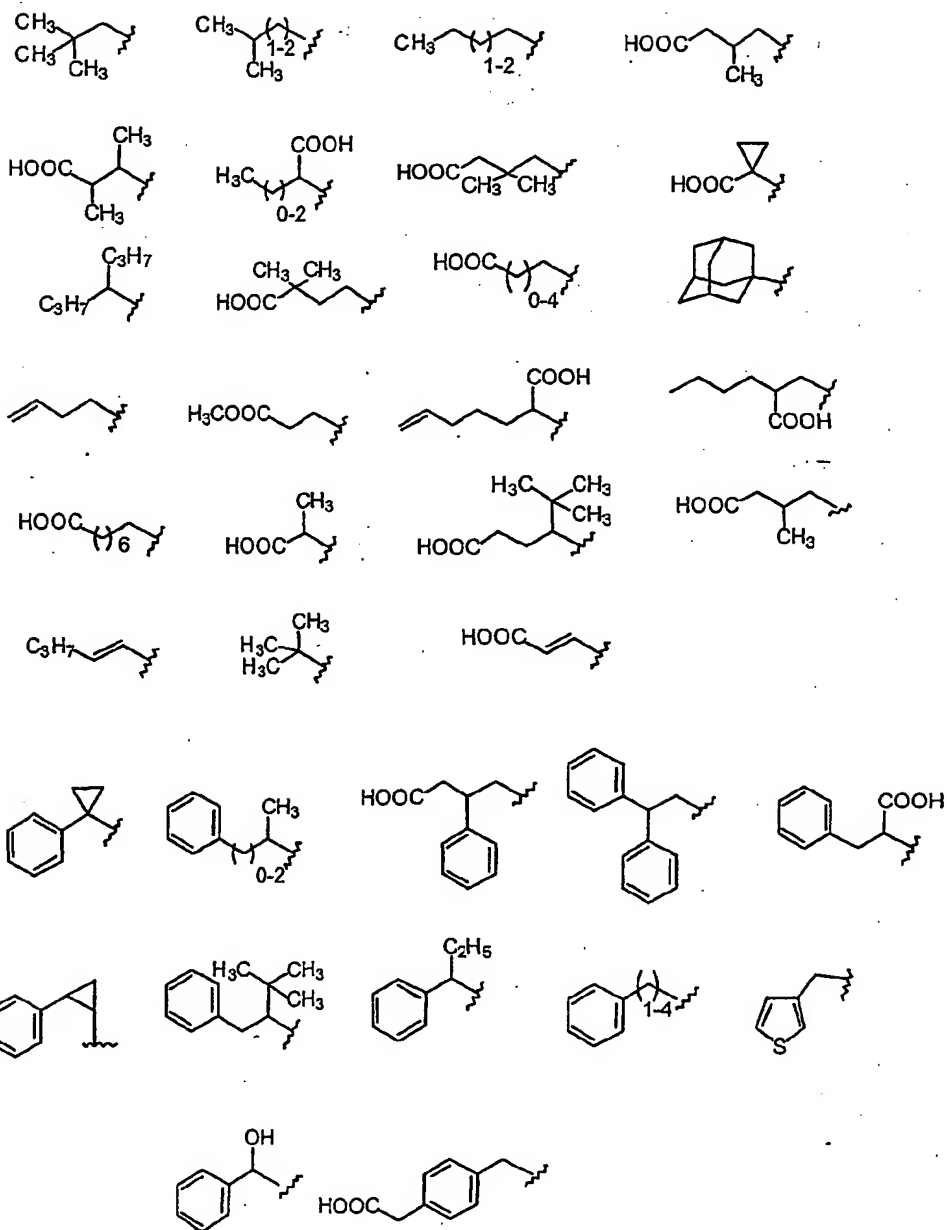


wherein $R^{31} = \text{OH}$ or O-alkyl.

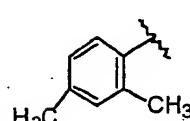
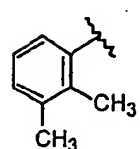
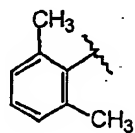
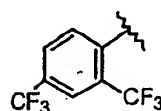
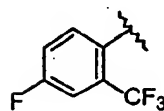
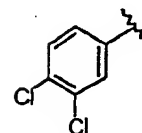
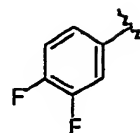
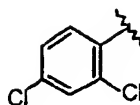
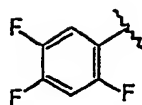
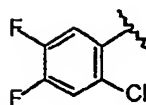
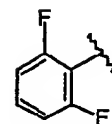
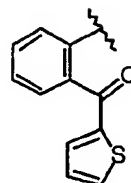
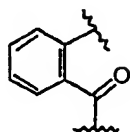
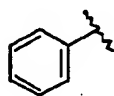
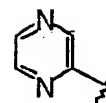
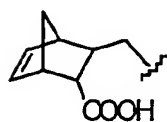
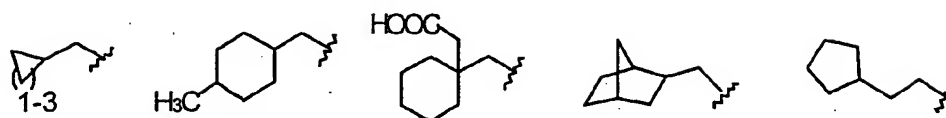
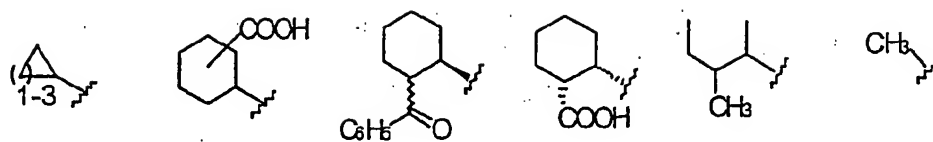
40. The compound of Claim 29, wherein U is N and P⁴ is alkyl or arylalkyl.
41. The compound according to Claim 29, wherein U is O or CH₂.
42. The compound according to Claim 29, wherein P⁴ is selected from
- 5 the following moieties:



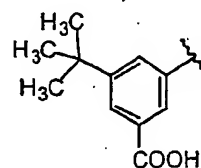
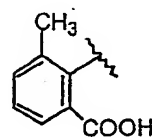
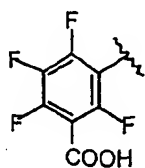
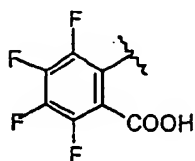
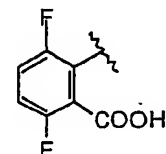
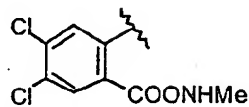
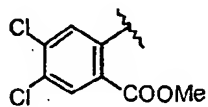
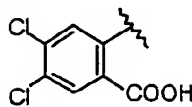
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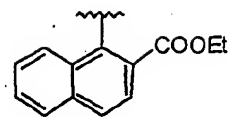
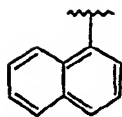
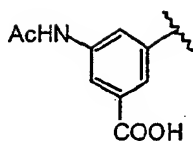
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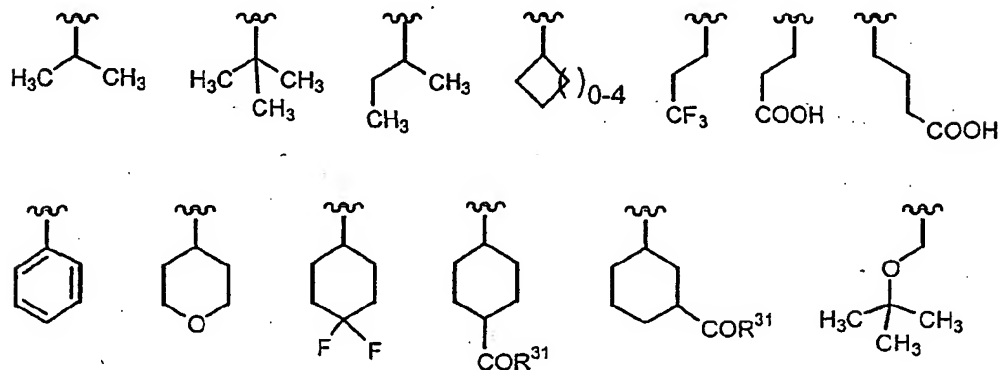
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43. The compound according to Claim 42, wherein U is CH₂ and P⁴ is
 5 phenyl.
44. The compound according to Claim 42, wherein U is O and P⁴ is
 selected from the group consisting of methyl, tertiary butyl, isobutyl, and
 2,3-dimethylpropyl.
45. The compound according to Claim 42, wherein P² and P³ are
 10 independently selected from the group consisting of: H, linear alkyl,
 branched alkyl, or arylalkyl, such that P² or P³ and the adjacent nitrogen
 and carbonyl moieties thereto correspond to the residuum of an alpha
 amino acid.
46. The compound according to Claim 45, wherein P³ is selected from
 15 the following moieties:

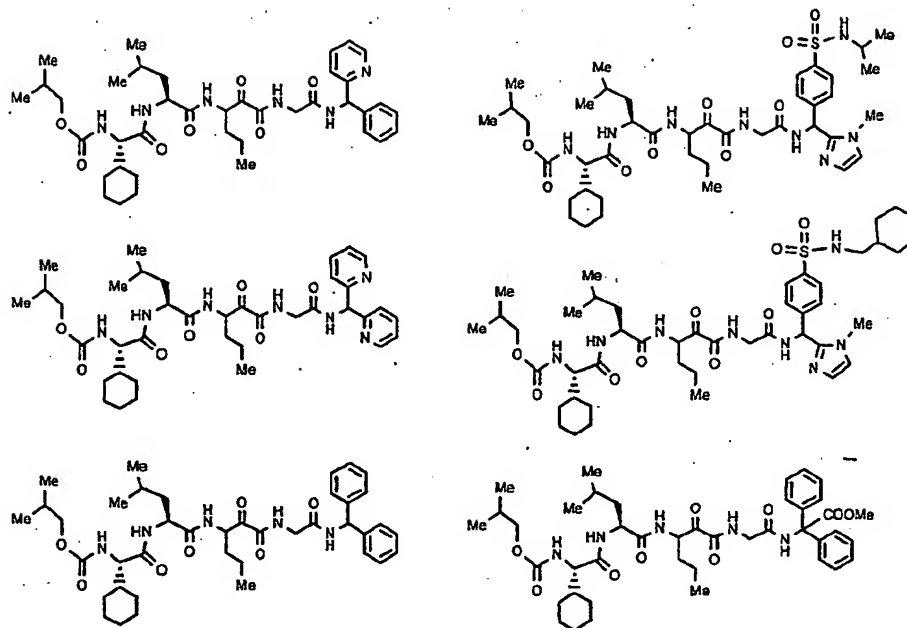


wherein R³¹ = OH or O-alkyl.

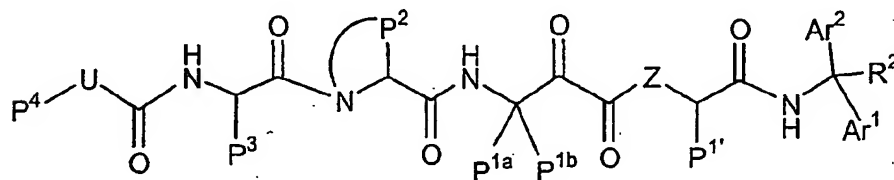
- 20 47. The compound according to Claim 46, wherein P³ is selected from
 the group consisting of isopropyl, tertiary butyl, isobutyl, and cyclohexyl
 substituents.

48. The compound of Claim 45, wherein V is H.
49. A pharmaceutical composition comprising as an active ingredient a compound of Claim 29.
50. The pharmaceutical composition of Claim 49 for use in treating disorders associated with HCV.
51. The pharmaceutical composition of Claim 49 additionally comprising a pharmaceutically acceptable carrier.
52. The pharmaceutical composition of Claim 51, additionally containing an antiviral agent.
53. The pharmaceutical composition of Claim 52, still additionally containing an interferon.
54. The pharmaceutical composition of Claim 53, wherein said antiviral agent is ribavirin and said interferon is α -interferon.
55. A method of treating disorders associated with the HCV virus, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of a compound of Claim 29.
56. The method of Claim 55, wherein said administration is subcutaneous.
57. The use of a compound of Claim 29 for the manufacture of a medicament to treat disorders associated with the HCV virus.
58. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV virus, said method comprising bringing into intimate contact a compound of Claim 29 and a pharmaceutically acceptable carrier.
59. A compound exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said compound being selected from the compounds of structures listed below:

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60. A compound, including enantiomers, stereoisomers, rotomers and tautomers of said compound, and pharmaceutically acceptable salts, solvates or derivatives thereof, with said compound having the general structure shown in Formula III:



Formula III

wherein:

- 10 P^{1a} , P^{1b} , $P^{1'}$, P^2 , and P^3 are independently selected from:

H, C1-C10 straight or branched chain alkyl, C2-C10 straight or branched chain alkenyl; and C3-C8 cycloalkyl, C3-C8 heterocyclic; (cycloalkyl)alkyl or (heterocyclyl)alkyl, wherein said cycloalkyl is made up of 3 to 8 carbon atoms, and zero to 6 oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of 1 to 6 carbon atoms;

15

- aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein said alkyl is of 1 to 6 carbon atoms;
wherein said alkyl, alkenyl, cycloalkyl, heterocyclyl; (cycloalkyl)alkyl and (heterocyclyl)alkyl moieties may be optionally substituted with Rⁿ, and
5 further wherein said P^{1a} and P^{1b} may optionally be joined to each other to form a spirocyclic or spiroheterocyclic ring, with said spirocyclic or spiroheterocyclic ring containing zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and may be additionally optionally substituted with Rⁿ;
Rⁿ is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino,
10 arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro moiety, with the proviso that the alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from Rⁿ;
15 Z is O, NH or NR^m;
R^m is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl moiety, with the proviso that R^m may be additionally optionally substituted with Rⁿ;
20 Ar¹ and Ar² are independently selected from phenyl; 2-pyridyl, 3-pyridyl, 4-pyridyl or their corresponding N-oxides; 2-thiophenyl; 3-thiophenyl; 2-furanyl; 3-furanyl; 2-pyrrolyl; 3-pyrrolyl; 2-imidazolyl; 3(4)-imidazolyl; 3-(1,2,4-triazolyl); 5-tetrazolyl; 2-thiazolyl; 4-thiazolyl; 2-oxazolyl; or 4-oxazolyl; either or both of which may be optionally substituted with R¹;
25 R¹ is H, halogen, cyano, nitro, CF₃, Si(alkyl)₃, straight-chain or branched lower alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl, hydroxy, alkoxy, aryloxy, alkoxycarbonyloxy, (alkylamino)carbonyloxy, mercapto, alkylthio, arylthio, alkylsulfinyl, heterocyclylsulfinyl, arylsulfinyl, heteroarylsulfinyl, alkylsulfonyl,
30 heterocyclylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl,

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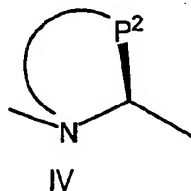
arylcarbonyl, carboxy, alkoxycarbonyl, aryloxy carbonyl,
 heteroaryloxy carbonyl, alkyaminocarbonyl, arylaminocarbonyl, amino,
 alkylamino, arylamino, alkylsulfonamido, arylsulfonamido,
 alkoxycarbonbylamino, alkylureido, or arylureido;

5 P^4 is H, linear or branched alkyl, arylalkyl or aryl;

R^2 is H, cyano, CF_3 , straight-chain or branched lower alkyl, alkenyl,
 alkynyl, cycloalkyl, cycloalkyl-alkyl, aryl, alkylaryl, arylalkyl, heteroaryl,
 alkylsulfonyl, arylsulfonyl, carboxy, alkoxycarbonyl, aryloxy carbonyl,
 alkyaminocarbonyl, (allylamino)carbonyl, or arylaminocarbonyl;

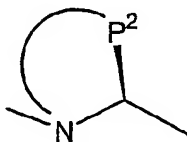
10 U is O, NH, CH_2 or CHR'' ;

and



15 where moiety IV indicates a cyclic ring structure, with the proviso that said
 cyclic ring structure does not contain a carbonyl group as part of the cyclic
 ring.

61. The compound of Claim 60, wherein said

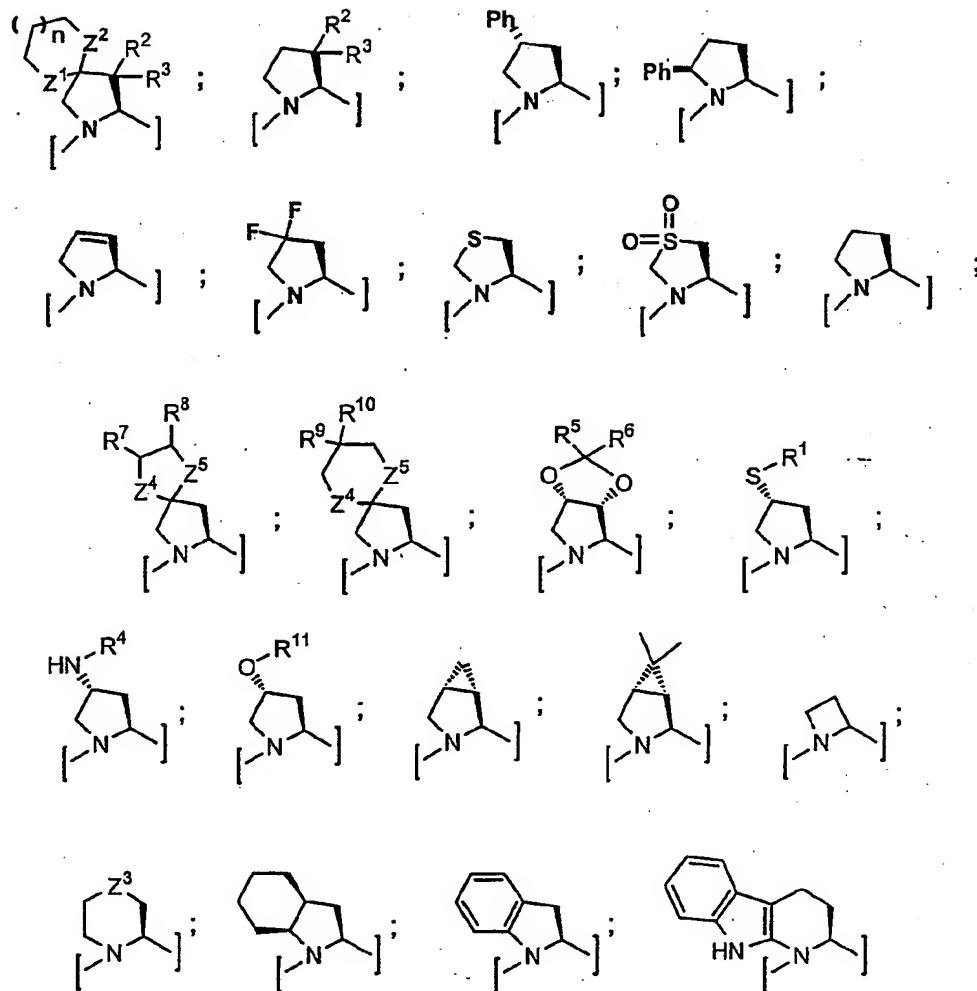


indicates a five-membered ring or a six-membered ring.

62. The compound of Claim 60, wherein the moiety IV forms a
 structural unit selected from the group consisting of:

25

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wherein $n = 0, 1, 2$ or 3 ; and

5

$R^2 = R^3 = H$; $R^2 = C_1$ to C_6 straight chain alkyl or cycloalkyl; $R^3 = H$

$R^4 = COAlkyl$ (straight chain or cyclic, C_1 to C_6); $COAryl$; $COOAlkyl$; $COOAryl$, SO_2Alkyl ; or SO_2Aryl .

$R^5 = H$; $R^6 = Alkyl$ (C_1 to C_3); $R^6 = H$; $R^5 = Alkyl$ (C_1 to C_3)

$R^7 = H$; $R^8 = Alkyl$ (C_1 to C_3), CH_2OH ; $R^8 = H$; $R^7 = Alkyl$ (C_1 to C_3), CH_2OH ;

$R^9 = R^{10} = Alkyl$ (C_1 to C_3); $R^9 = H$, $R^{10} = Alkyl$ (C_1 to C_3), $COOMe$, $COOH$, CH_2OH ;

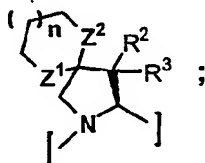
10 $R^{10} = H$, $R^9 = Alkyl$ (C_1 to C_3), $COOMe$, $COOH$, CH_2OH ;

R^{11} = Alkyl (C_1 to C_6 straight chain, branched or cyclic), CH_2 Aryl (may be substituted)

X^1 = H, Alkyl (C_1 to C_4 , branched or straight chain); CH_2 Aryl (substituted or unsubstituted)

- 5 $Z^1 = Z^2 = S, O$; $Z^1 = S, Z^2 = O$; $Z^1 = O, Z^2 = S$; $Z^1 = CH_2, Z^2 = O$; $Z^1 = O, Z^2 = CH_2$; $Z^1 = S, Z^2 = CH_2$; $Z^1 = CH_2, Z^2 = S$; $Z^3 = CH_2, S, SO_2, NH, NR^4$; $Z^4 = Z^5 = S, O$.

63. The compound according to Claim 62, wherein said cyclic ring
10 moiety is:



wherein Z^1 and Z^2 are S, R^2 and R^3 are H and $n=1$ or 2.

64. The compound according to Claim 63, wherein $R^{2'}$ is selected from
the group consisting of H, alkyl, alkenyl, alkoxy carbonyl, or (allylamino)
15 carbonyl.

65. The compound according to Claim 64, wherein $R^{2'}$ is H.

66. The compound according to Claim 63, wherein Ar^1 and Ar^2 are
independently selected from the group consisting of phenyl, 2-thiophenyl,
2-furanyl, 3-furanyl, 3(4)-imidazolyl, 3-(1,2,4-triazolyl), 5-tetrazolyl, or 2-
20 thiazolyl.

67. The compound according to Claim 66 wherein Ar^2 is phenyl and Ar^1
is selected from the group consisting of 3-(1,2,4-triazolyl), 5-tetrazolyl, or 2-
thiazolyl.

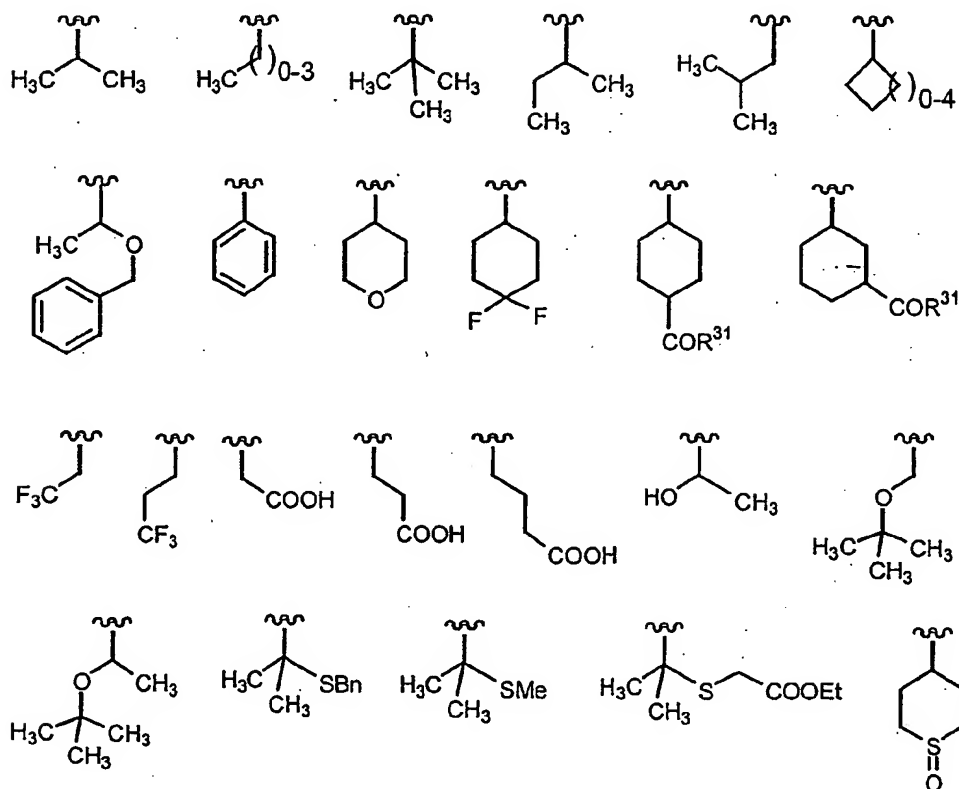
68. The compound according to Claim 63, wherein R^1 is H, CF_3 , CH_3 ,
25 alkyl or alkenyl.

69. The compound according to Claim 63, wherein $P^{1'}$ is selected from
the group consisting of H, F or CH_3 .

70. The compound according to Claim 63, wherein $P^{1'}$ is H such that $P^{1'}$
and the adjacent nitrogen and carbonyl moieties correspond to the
30 residuum of glycine unit.

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72. The compound according to Claim 63, wherein P^3 is selected from the group consisting of:



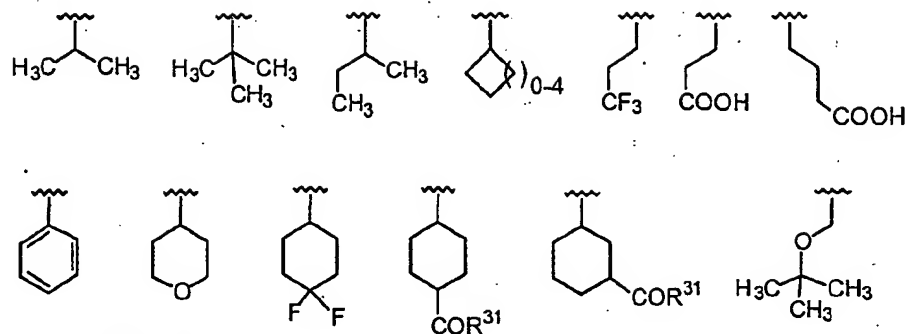
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wherein R^{31} = OH or O-alkyl.

73. The compound of Claim 72, wherein R^3 is selected from the group consisting of the following moieties:

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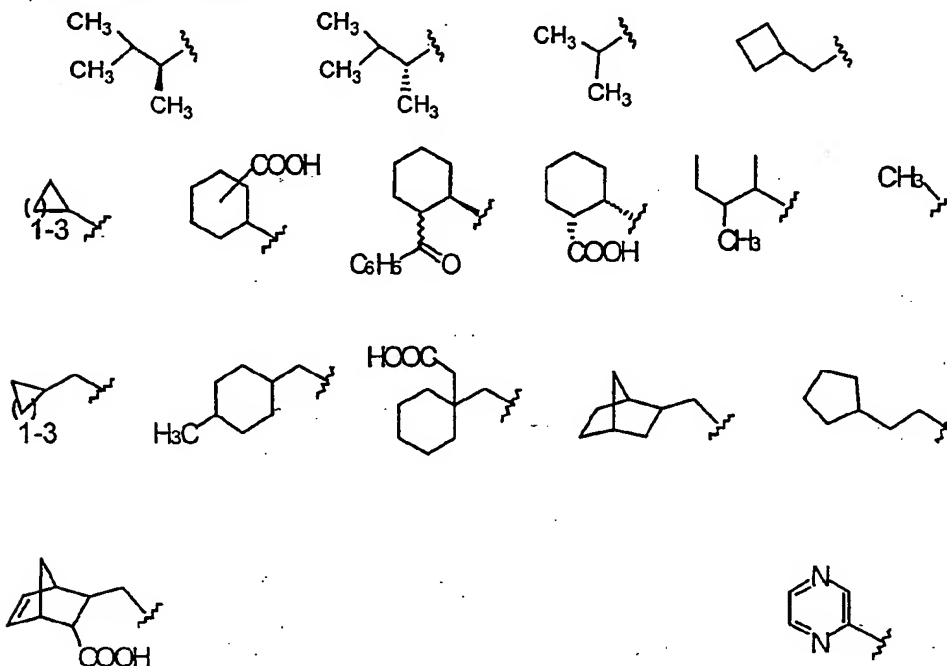


wherein $R^{31} = \text{OH}$ or O-alkyl.

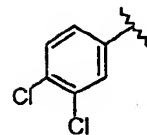
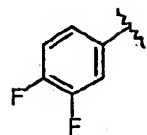
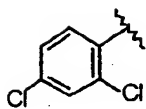
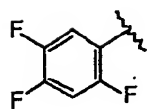
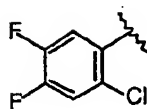
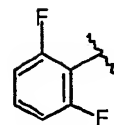
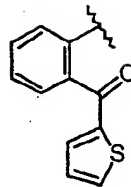
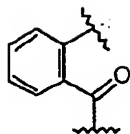
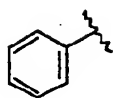
74. The compound of Claim 63, wherein U is NH and P^4 is alkyl or arylalkyl.

5 75. The compound according to Claim 63, wherein U is O or CH_2 .

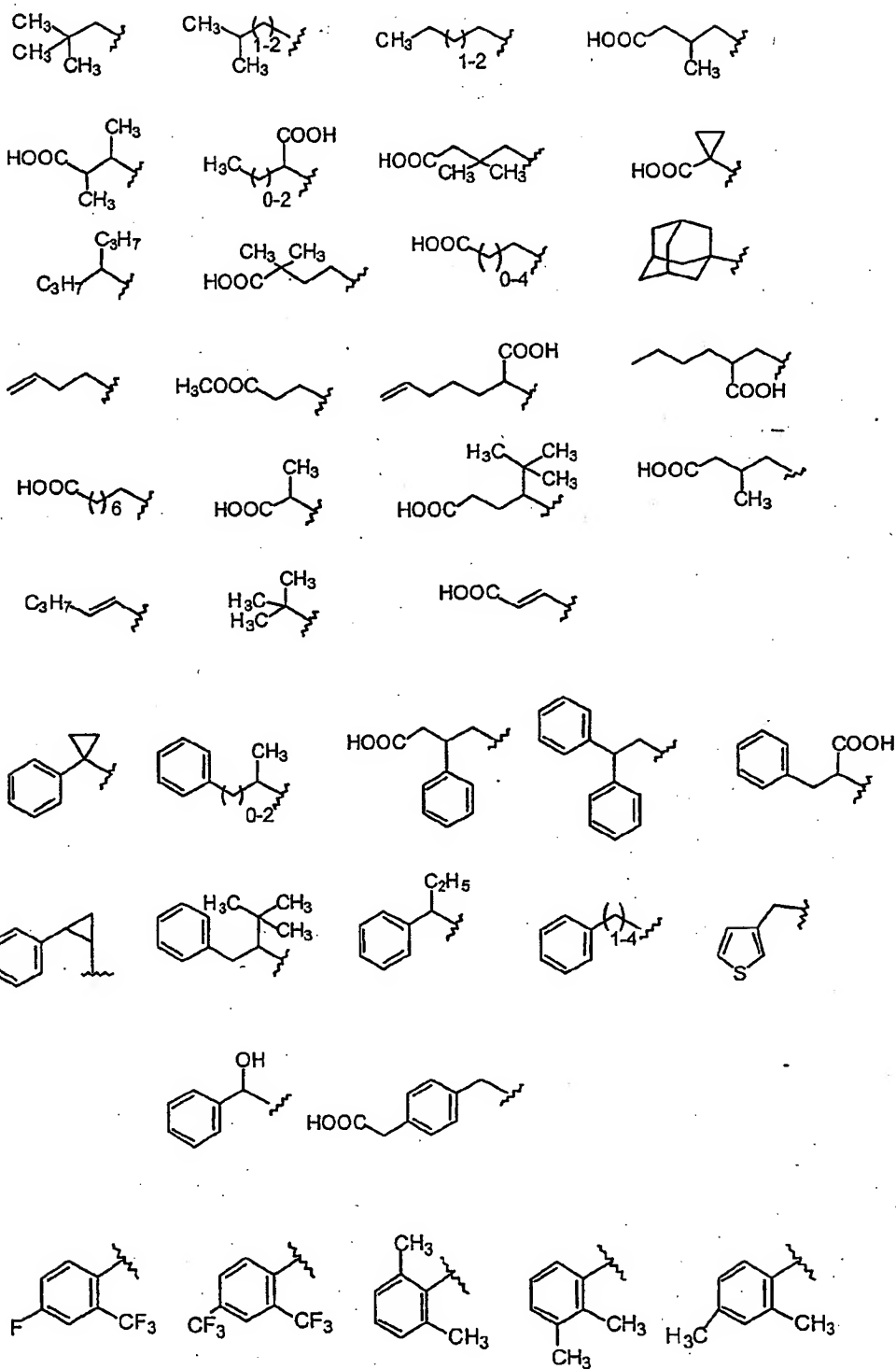
76. The compound according to Claim 63, wherein P^4 is selected from the following moieties:



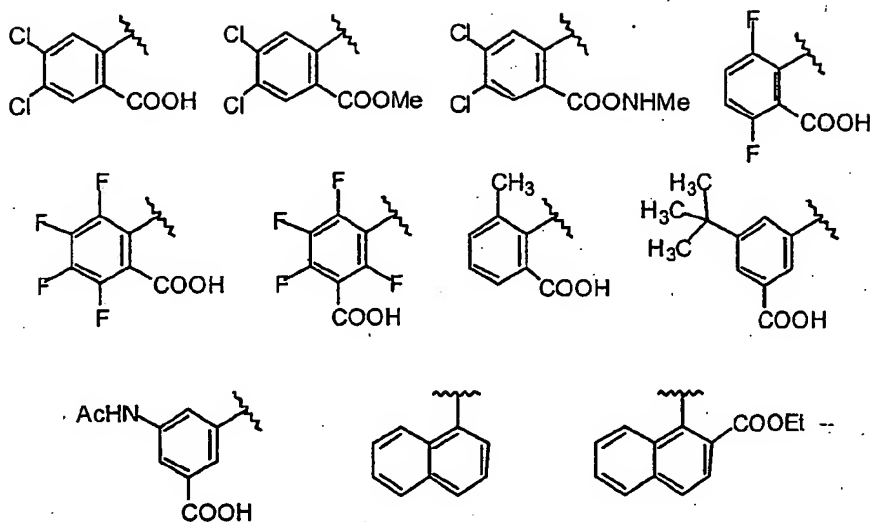
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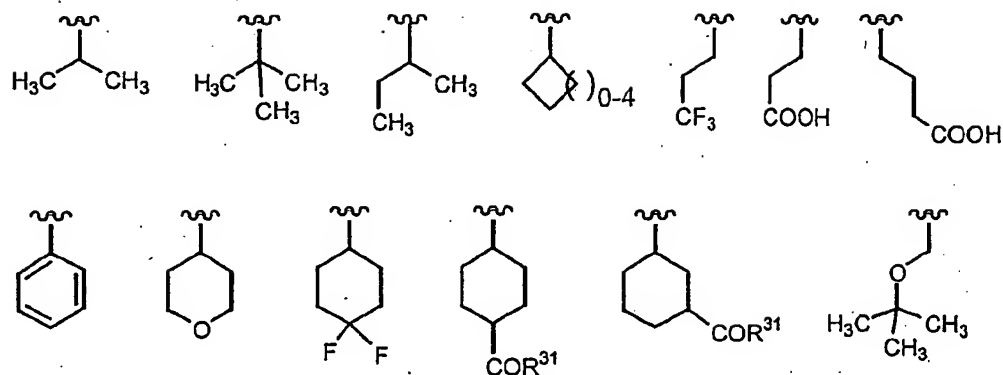
77. The compound according to Claim 76, wherein U is CH₂ and P⁴ is phenyl.

78. The compound according to Claim 76, wherein U is O and P⁴ is selected from the group consisting of methyl, tertiary butyl, isobutyl, and 2,3-dimethylpropyl.

79. The compound according to Claim 76 wherein P² and P³ are independently selected from the group consisting of: H, linear alkyl, branched alkyl, or arylalkyl, such that P² OR P³ and the adjacent nitrogen and carbonyl moieties thereto correspond to the residuum of an alpha amino acid.

80. The compound according to Claim 79, wherein P³ is selected from the following moieties:

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wherein $R^{31} = \text{OH}$ or O-alkyl.

81. The compound according to Claim 80, wherein P^3 is selected from the group consisting of isopropyl tertiary butyl, isobutyl and cyclohexyl substituents.
82. A pharmaceutical composition comprising as an active ingredient a compound of Claim 60.
83. The pharmaceutical composition of Claim 82 for use in treating disorders associated with HCV.
84. The pharmaceutical composition of Claim 82 additionally comprising a pharmaceutically acceptable carrier.
85. The pharmaceutical composition of Claim 84, additionally containing an antiviral agent.
86. The pharmaceutical composition of Claim 85, still additionally containing an interferon.
87. The pharmaceutical composition of Claim 86, wherein said antiviral agent is ribavirin and said interferon is α -interferon.
88. A method of treating disorders associated with the HCV virus, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of a compound of Claim 60.
89. The method of Claim 88, wherein said administration is subcutaneous.

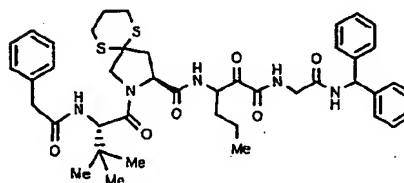
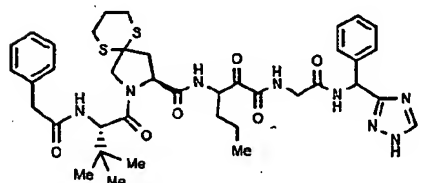
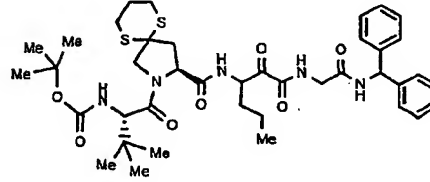
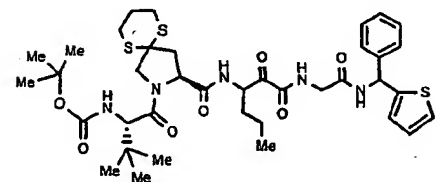
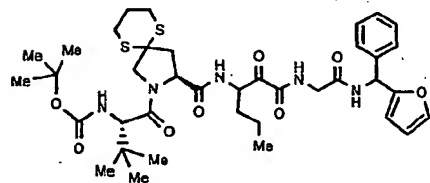
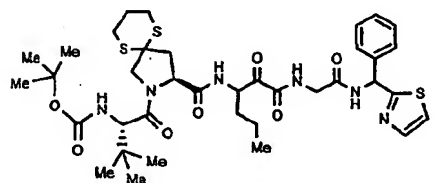
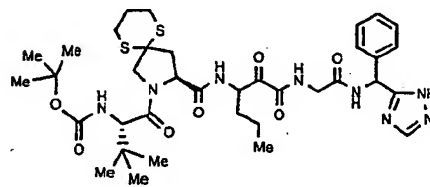
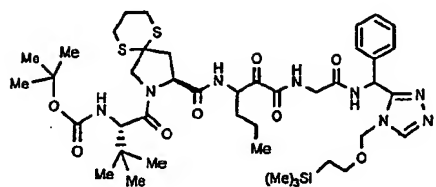
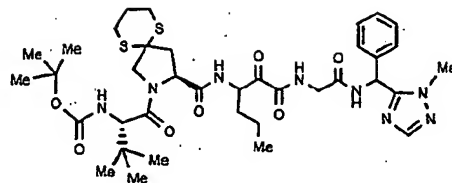
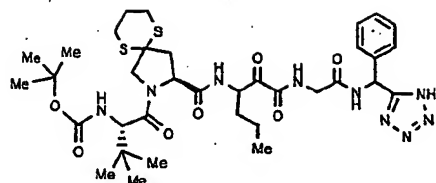
90. The use of a compound of Claim 60 for the manufacture of a medicament to treat disorders associated with the HCV virus.

91. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV virus, said method comprising
5 bringing into intimate contact a compound of Claim 60 and a pharmaceutically acceptable carrier.

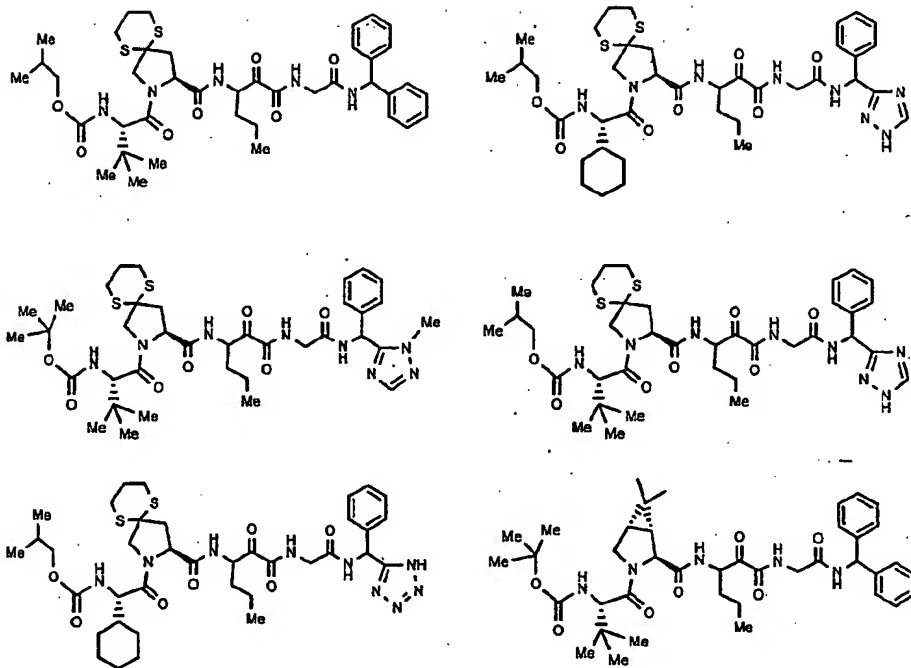
92. A compound exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers and tautomers of said compound, and pharmaceutically acceptable salts or solvates of said compound, said
10 compound being selected from the compounds of structures listed in Claim 60.

93. The compound according to Claim 60, wherein said compound is selected from the group consisting of:

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94. A pharmaceutical composition for treating disorders associated with the HCV virus, said composition comprising therapeutically effective amount of one or more compounds in Claim 93 and a pharmaceutically

5 acceptable carrier.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
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(10) International Publication Number
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(51) International Patent Classification⁷: C07K 14/81,
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(74) Agent: KALYANARAMAN, Palaiyur, S.; Schering-Plough Corporation, Patent Department-K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(21) International Application Number: PCT/US01/47383

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10 December 2001 (10.12.2001)

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(71) Applicant: SCHERING CORPORATION [US/US];
Patent Department - K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

Declaration under Rule 4.17:

— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations

Published:

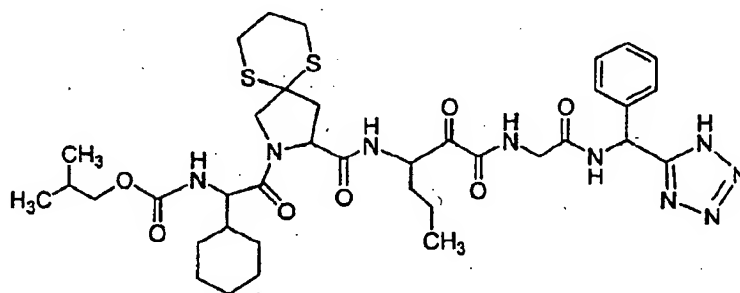
— with international search report

(88) Date of publication of the international search report:
19 June 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(72) Inventors: ZHU, Zhaoning; 1704 Quail Ridge Drive, Plainsboro, NJ 08536 (US). SUN, Zhong-Yue; 12 Stratton Court, Parlin, NJ 08859 (US). VENKATRAMAN, Srikanth; 35 Roanoke Street, Woodbridge, NJ 07095 (US). NJORGE, F. George; 11 Softwood Way, Warren, NJ 07059 (US). ARASAPPAN, Ashok; 18 Larsen Court, Bridgewater, NJ 08807 (US). MALCOLM, Bruce, A.; 515 Trinity Place, Apt., 3BN, Westfield, NJ 07090 (US). GIRIJAVALLABHAN, Viyyoor, M.; 10 Maplewood Drive, Parsippany, NJ 07054 (US). LOVEY, Raymond, G.; 65 Woodside Avenue, West Caldwell, NJ 07006 (US). CHEN, Kevin, X.; 9 Gloria Avenue, Edison, NJ 08820 (US).

(54) Title: DIARYL PEPTIDES AS NS3-SERINE PROTEASE INHIBITORS OF HEPATITIS C VIRUS



(57) Abstract: The present invention is directed to certain diaryl amide compounds as NS3-Serine protease inhibitors of hepatitis C virus. A particularly preferred compound is of the formula (I).

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/US 01/47383

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07K14/81 C07K5/08 A61K38/06 A61P31/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 17679 A (DEININGER DAVID D ;MURCKO MARK A (US); VERTEX PHARMA (US); FARMER) 30 April 1998 (1998-04-30)	29-94
A	claims 1,35; examples 78-80,101-123; tables 2-4	1-28
E	WO 02 08187 A (SCHERING CORP ;CORVAS INT INC (US)) 31 January 2002 (2002-01-31) claim 1; example 20; table 2	29-59
E	WO 02 08244 A (SCHERING CORP ;CORVAS INT INC (US)) 31 January 2002 (2002-01-31) claim 1; example 716; table 5	60-94
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

13 December 2002

Date of mailing of the international search report

31/01/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
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Authorized officer

Fausti, S

INTERNATIONAL SEARCH REPORT

Internal application No
PCT/US 01/47383

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LLINAS-BRUNET ET AL: "Studies on the C-terminal of hexapeptide inhibitors of the hepatitis C virus serine protease" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 19, 6 October 1998 (1998-10-06), pages 2719-2724, XP002199470 ISSN: 0960-894X abstract; table 1	1-94

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/47383

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 24, 25, 55, 56, 88, 89
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 24,25,55,56,88,89 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 24,25,55,56,88,89

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

In: tion on patent family members

Internat Application No
PCT/US 01/47383

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9817679	A	30-04-1998	AP 1019 A 16-10-2001
			AT 212037 T 15-02-2002
			AU 719984 B2 18-05-2000
			AU 5147798 A 15-05-1998
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			DE 69709671 D1 21-02-2002
			DE 69709671 T2 22-08-2002
			DK 932617 T3 22-04-2002
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			EP 0932617 A1 04-08-1999
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			SK 51099 A3 10-04-2000
			TR 9901602 T2 21-10-1999
			WO 9817679 A1 30-04-1998
			US 6265380 B1 24-07-2001
			US 2002032175 A1 14-03-2002
			ZA 9709327 A 11-05-1998
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			WO 0208187 A1 31-01-2002
			US 2002160962 A1 31-10-2002
WO 0208244	A	31-01-2002	AU 7698801 A 05-02-2002
			WO 0208244 A2 31-01-2002